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ANTIPHOSPHOLIPID SYNDROME: EXPANDING THE SPECTRUM OF AUTOIMMUNE THROMBOSIS

PhD THESIS

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2. **Gómez-Puerta JA**, Cervera R, Gil V. “Catastrophic" antiphospholipid syndrome. Mayo Clin Proc 2003 ;78:519

3. Cervera R, Asherson RA, Acevedo ML, **Gómez-Puerta JA**, Espinosa G, De La Red G et al. Antiphospholipid syndrome associated with infections: clinical and microbiological characteristics of 100 patients. Ann Rheum Dis 2004; 63:1312-1317.

4. **Gómez-Puerta JA**, Cervera R, Calvo LM, Gómez-Anson B, Espinosa G, Claver G et al. Dementia associated with the antiphospholipid syndrome: clinical and radiological characteristics of 30 patients. Rheumatology (Oxford) 2005;44:95-99.

5. Cervera R, Font J, **Gómez-Puerta JA**, Espinosa G, Cucho M, Bucciarelli S et al. Validation of the preliminary criteria for the classification of catastrophic antiphospholipid syndrome. Ann Rheum Dis 2005;64:1205-1209.

6. Asherson RA, Espinosa G, Cervera R, **Gómez-Puerta JA**, Musuruana J, Bucciarelli S et al. Disseminated intravascular coagulation in catastrophic antiphospholipid syndrome: clinical and haematological characteristics of 23 patients. Ann Rheum Dis 2005;64:943-946.

7. Asherson RA, **Gómez-Puerta JA**, Marinopoulos G. Recurrent pulmonary thromboembolism in a patient with systemic lupus erythematosus and HIV-1 infection associated with the presence of antibodies to prothrombin: a case report. Clin Inf Dis 2005; 41:e89–92

8. Cervera R, **Gómez-Puerta JA**, Blank M, Asherson RA, Shoenfeld Y. Autoinmunidad e infección: Hipótesis del mimetismo molecular. En autoinmunidad y enfermedad autoinmune. Anaya JM, Shoenfeld Y, Correa P, García Carrasco M y Cervera R. Ed. CIB 2005:pp 231-242.

9. Bucciarelli S, Espinosa G, Asherson RA, Cervera R, Claver G, **Gómez-Puerta JA** et al. The acute respiratory distress syndrome in catastrophic antiphospholipid syndrome: analysis of a series of 47 patients. Ann Rheum Dis 2006 ;65:81-86.

10. **Gómez-Puerta JA**, Salgado E, Cervera R, Aguilo S, Ramos-Casals M, Soler M et al. Catastrophic antiphospholipid syndrome presenting with renal thrombotic microangiopathy and diffuse proliferative glomerulonephritis. Clin Exp Rheumatol 2006;24:110.

11. Rees JD, Lanca S, Marques PV, **Gómez-Puerta JA**, Moco R, Oliveri C et al. Prevalence of the antiphospholipid syndrome in primary systemic vasculitis. Ann Rheum Dis 2006;65:109-111.

12. Bucciarelli S, Espinosa G, Cervera R, Erkan D, **Gómez-Puerta JA**, Ramos-Casals M et al. Mortality in the catastrophic antiphospholipid syndrome: causes of death and prognostic factors in a series of 250 patients. Arthritis Rheum 2006;54:2568-2576

13. Espinosa G, Bucciarelli S, Cervera R, **Gómez-Puerta JA**, Font J. Laboratory studies on pathophysiology of the catastrophic antiphospholipid syndrome. Autoimmun Rev 2006;6:68-71

14. Bucciarelli S, Cervera R, Espinosa G, **Gómez-Puerta JA**, Ramos-Casals M, Font J. Mortality in the catastrophic antiphospholipid syndrome: causes of death and prognostic factors. Autoimmun Rev 2006 ;6:72-75.

15. Cervera R, Espinosa G, Bucciarelli S, **Gómez-Puerta JA**, Font J. Lessons from the catastrophic antiphospholipid syndrome (CAPS) registry. Autoimmun Rev 2006 ;6:81-84

16. **Gómez-Puerta JA**, Cervera R, Espinosa G, Bucciarelli S, Font J. Pregnancy and puerperium are high susceptibility periods for the development of catastrophic antiphospholipid syndrome. Autoimmun Rev 2006;6:85-88.

17. Miesbach W, Asherson RA, Cervera R, Shoenfeld Y, **Gómez-Puerta JA**, Bucciarelli S et al. The catastrophic antiphospholipid (Asherson's) syndrome and malignancies. Autoimmun Rev 2006 ;6:94-97.

18. Miesbach W, Asherson RA, Cervera R, Shoenfeld Y, **Gómez-Puerta JA**, Espinosa G, Bucciarrelli S; Members of the CAPS Registry Group. The role of malignancies in patients

with catastrophic anti-phospholipid (Asherson's) syndrome. Clin Rheumatol. 2007 May 24; [Epub ahead of print]

19. García-Carrasco M, Galarza C, Gómez-Ponce M, Cervera R, Rojas-Rodiguez J, Espinosa G, Bucciarelli S, **Gómez-Puerta JA**, Bové A, Escarcega RO, Font J. Antiphospholipid syndrome in Latin American patients: clinical and immunologic characteristics and comparison with European patients. Lupus 2007;16:366-373.

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1. ABBREVIATIONS

aCL:	Anticardiolipin antibodies
AIHA:	Autoimmune hemolytic anemia
ANAs:	Antinuclear antibodies
Anti-dsDNA:	Anti double stranded DNA antibodies
Anti-ENA:	Antiextractable nuclear antigen antibodies
Anti-oxLDL:	Anti oxidized low density lipoprotein antibodies
Anti-PT:	Anti prothrombin antibodies
aPS-PT:	Anti phosphatidylserine-prothrombin complex antibodies
aPL:	Antiphospholipid antibodies
APS:	Antiphospholipid syndrome
ARDS:	Acute respiratory distress syndrome
β2GPI:	β2-glycoprotein I
CAPS:	Catastrophic antiphospholipid syndrome
CNS:	Central nervous system
DIC:	Disseminated intravascular coagulation
DVT:	Deep vein thrombosis
ICAM-1:	Intercellular cell adhesion molecule-1
ICU:	Intensive care unit
HCV:	Hepatitis C virus
HELLP:	Hemolysis, elevated liver enzymes and low platelets
HIV:	Human immunodeficiency virus
LA:	Lupus anticoagulant
LLD:	Lupus-like disease
LMWH	Low molecular-weight heparins
MI:	Myocardial infarction

MRI:	Magnetic resonance imaging
MS:	Multiple sclerosis
NHL	Non-Hodgkin lymphoma
PE:	Pulmonary embolism
pSS:	Primary Sjögren syndrome
PSV:	Primary systemic vasculitis
RA:	Rheumatoid arthritis
RF:	Rheumatoid factor
SLE:	Systemic lupus erythematosus
Spa:	Spondyloarthropathies
SSc:	Systemic sclerosis
TTE	Transthoracic echocardiography
TEE:	Transesophageal echocardiography
TIA:	Transient ischemic attack
TMA:	Thrombotic microangiopathy
TF:	Tissue factor
TNF-α:	Tumour necrosis factor-α
VCAM-1:	Vascular cell adhesion molecule-1

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3. INTRODUCTION

HISTORICAL PERSPECTIVE

In 1906, Wasserman and colleagues (1) discovered “reagin” an antibody reacting with an antigen located in alcohol extracts of liver from a fetus with congenital syphilis. Pangborn (2), in 1941, showed that this antigen was a phospholipid wich was named cardiolipin. The subsequent use of cardiolipin, together with phosphatidylcholine and cholesterol, led to the development of various precipitation complement fixation techniques to detect reagin. During Word War II, individuals with positive serologic test results for syphilis were identified, but they had no clinical evidence of the disease. It became apparent that false-positive serologic test results for syphilis might occur occasionally, usually as a result of an acute infection such as malaria or endocarditis. In 1955, it was shown that patients with endocarditis had a high incidence of autoimmune disorders, especially systemic lupus erythematosus (SLE) (3).

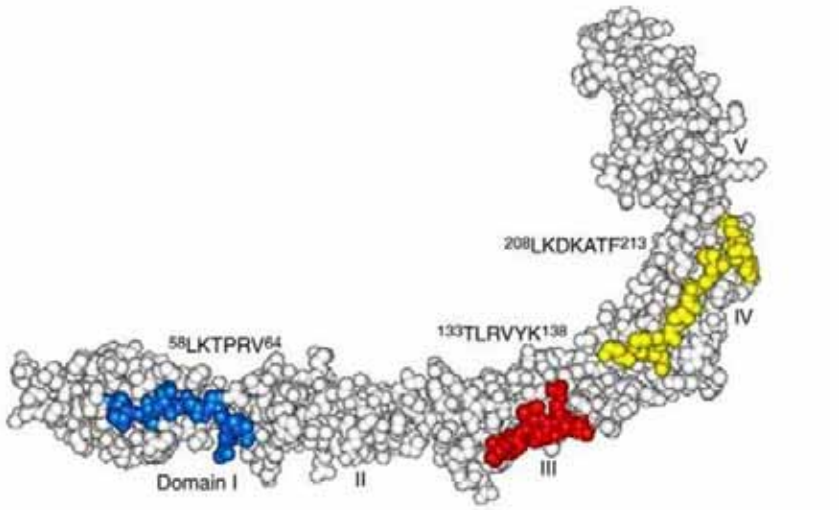
In 1952, an *in vitro* inhibitor of coagulation was found in two patients with SLE. This inhibitor was frequently associated with false-positive serologic test results for syphilis and could be absorbed from plasma by phospholipids (4). In 1972, it was named lupus anticoagulant (LA), although 50 percent of patients with this serologic abnormality do not have SLE. Although the antibody acts as an anticoagulant *in vitro*, *in vivo* it is mainly associated with thrombotic events and less frequently with hemorrhage (5).

In the early 1980s, studies carried out at London’s Hammersmith Hospital by Dr Graham Hughes and colleagues, led to the development of solid-phase immunoassays to detect anticardiolipin (aCL) (6). A high correlation between the IgG isotype of aCL and clinical thrombosis was documented and a close relationship between these antibodies and the presence of the LA was also demonstrated (7). In 1986, these findings led to the recognition of the so-called anticardiolipin syndrome, which was later more correctly named the antiphospholipid syndrome (APS) or Hughes syndrome. In 1987, Dr Hughes group recognized

that some individuals without lupus or antinuclear antibodies (ANAs) developed the syndrome. These patients were termed as primary APS.

A major advance came in the early 1990s with the simultaneous recognition by three different groups that antiphospholipid antibodies (aPL) required a plasma protein "cofactor" to bind cardiolipin on ELISA plates. ß2-glycoprotein I (β_2GPI) was identified as this cofactor (Figure 1). Since then, a number of "cofactors", including prothrombin, have been described. In 1992, Dr Ronald Asherson described for the first time a subgroup of patients with an unusual form of presentation of APS with a widespread coagulopathy affecting predominantly small vessels that led to rapid multiorgan failure. This dramatic clinical situation was termed catastrophic APS (CAPS) (8).

Figure 1. Structure and peptide localization of β_2GPI



In 1999, a preliminary classification criteria was established after an expert workshop held in Sapporo, Japan (9) (Table 1). The need for consensus criteria for APS was heightened by the diversity of clinical and basic science disciplines that contribute to the diagnosis and treatment of APS and by the lack of uniformity in previous proposed criteria for APS. These criteria have been validated and widely used in clinical trials during recent years.

Table 1. Preliminary classification criteria for APS (Sapporo Criteria)

Clinical criteria

1. Vascular thrombosis

   One or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ. Thrombosis must be confirmed by imaging or Doppler studies or histopathology, with the exception of superficial venous thrombosis. For histopathological confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.

2. Pregnancy morbidity

   (a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10^{th} week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or

   (b) One or more premature births of a morphologically normal neonate at or before the 34^{th} week of gestation because of severe preeclampsia or eclampsia, or severe placental insufficiency or

   (c) Three or more unexplained consecutive spontaneous abortions before the 10^{th} week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

Laboratory criteria

1. aCL of IgG and/or IgM isotype in blood, present in medium or high titers, on 2 or more occasions, at least 6 weeks apart, measured by a standardized enzyme-linked immunosorbent assay for β_2GPI –dependent anticardiolipin antibodies.

2. LA present in plasma, on 2 or more occasions at least 6 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Hemostasis.

Recently, another workshop was held in Sydney, Australia in which experts proposed some modifications to previous criteria, such as the inclusion of β_2GPI antibodies. Although no new clinical criteria were added, some particular features were remarked on, such as associated APS features, including cardiac valve involvement, *livedo reticularis*, thrombocytopenia, APS nephropathy and non-thrombotic central nervous system (CNS) manifestations (i.e., cognitive dysfunction) (Table 2) (10)

Table 2. Revised classification criteria for APS (Sydney Criteria)

Clinical criteria

1. Vascular thrombosis

   One or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ. Thrombosis must be confirmed by objective validated criteria (i.e. unequivocal findings of appropriate imaging studies or histopathology). For histopathological confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.

2. Pregnancy morbidity
   (a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10^{th} week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or

   (b) One or more premature births of a morphologically normal neonate before the 34^{th} week of gestation because of: (i) eclampsia or severe preeclampsia defined according to standard definitions, or (ii) recognized features of placental failure, or

   (c) Three or more unexplained consecutive spontaneous abortions before the 10^{th} week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

Laboratory criteria

1. LA present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Hemostasis

2. aCL antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high titers (i.e. >40 GPL or MPL, or >the 99^{th} percentile), on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA
3. Anti- β_2GPI antibody of IgG and/or IgM isotype in serum or plasma (in titers >the 99^{th} percentile), present on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA, according to recommended procedures.

APS is present if at least one of the clinical criteria and one of the laboratory criteria that follow are met

During recent years, the clinical spectrum of APS has extended to other fields, recognizing the presence of aPL in a series of other conditions such as systemic chronic infections, other autoinmune diseases (i.e., systemic vasculitis), malignancies or recurrent pregnancy losses.

More than 20 years after the original description of the clinical syndrome, there are still many questions unresolved, including the long term follow-up of patients with primary APS, the importance of aPL in asymptomatic patients and the clinical significance of these antibodies in other conditions such as malignancies.

APS can present in different scenarios, such as asymptomatic "carrier" patients for aPL, "classical" APS with recurrent venous and/ or arterial thrombosis, APS affecting otherwise healthy women with recurrent pregnancy loss, asymptomatic aPL positivity with non thrombotic aPL manifestations (i.e., thrombocytopenia, hemolytic anemia or livedo reticularis) or a life-threatening form characterized by a rapid development of microthombosis (CAPS) (11).

4.1 PATHOGENESIS

Several pathogenetic mechanisms for thrombosis in APS have been described. It is likely that no single mechanism explains thrombosis in it self. It is known that aPL are directed against phospholipid-binding proteins expressed on, or bound to, the surface of vascular endothelial cells or platelets. The main protein associated with aCL activity is β_2GPI bound to phospholipids. β_2GPI is a highly glycosylated single-chain protein that is present in plasma and avidly binds to negatively charged phospholipids such as cardiolipin, phosphatidylserine, or phosphatidylinositol. Despite the strong association between aPL and thrombosis, the pathogenic role of aPL in the development of thrombosis has not yet been fully elucidated. aPL interfere with several aspects of the protein C system, inhibiting the formation of thrombin (through the inhibition of prothrombinase activity), decreasing protein C activation by the thrombomodulin-thrombin complex, inhibiting assembly of the protein C complex, inhibiting activated protein C activity, and binding to factors Va and VIIIa in ways that protect them from proteolysis by activated protein C (11,12). Patients with aPL may also have antibodies directed against other proteins, including heparin/heparin sulfate, prothrombin, platelet-activating factor, tissue-type plasminogen activator, thromboplastin, oxidized low density lipoproteins, thrombomodulin, kininogen, factors VII, and XII (11,12).

aPL appear to play a direct pathogenic role and APS is now widely accepted as an example of an autoantibody-mediated disease. Proposed pathophysiological mechanisms may be categorized into two types. Firstly, aPL may act *in vivo* by disrupting hemostatic reactions occurring on cell membranes. aPL may alter the kinetics of the normal procoagulant and anticoagulant reactions by cross-linking membrane-bound proteins, by blocking protein-protein interactions, and/or by blocking the access of other proteins to the phospholipid membrane. Secondly, aPL may stimulate certain cells thereby altering the expression and secretion of various molecules (11).

It is accepted that aPL can react with endothelial cells, mainly through the binding to β_2GPI expressed on cell membranes. Exogenous β_2GPI can bind to endothelial cells at the putative phospholipid binding site located in the fifth domain of the molecule or through annexin II an endothelial cell receptor for tissue plasminogen activator. Anti β_2GPI can recognize cell membrane β_2GPI on either small or large vessel endothelial cells (12). Several effects of aPL on vascular endothelium have been described. aPL interact with cultured human vascular endothelial cells with resultant injury and/or activation. Incubation of cultured endothelial cells with aPL increases the expression of cell adhesion molecules [intercellular cell adhesion molecule-1 (ICAM-1), vascular cell adhesion-1 (VCAM-1) and E-selectin], an effect that is mediated by β_2GPI and may promote leukocyte adhesion to the endothelial surface. Tissue factor (TF) expression is increased in cultured endothelial cells incubated with aPL. aPL with reactivity against annexin V induce apoptosis in endothelial cells (12). LA have also been shown to stimulate the release of microparticles and possible prothrombotic activity from endothelial cells. aPL can also promote TF synthesis by leukocytes. Stimulation of peripheral blood monocytes from aPL syndrome patients with β_2GPI induces substantial monocyte TF activity. aPL may also increase TF activity via inhibition of TF pathway inhibitor activity (11,12).

Some animal studies suggest a pathogenetic role of aPL in pregnancy failure. Placental infarction is a feature of fetal loss in some cases of APS, suggesting a thrombotic pathogenesis. One postulated mechanism is that aPL displace annexin V (a potent anticoagulant protein) from trophoblasts with resulting increased exposure of anionic phospholipids and acceleration of thrombin generation. Annexin V appears to play a thrombomodulatory role in the placental circulation where it is necessary for maintenance of placental integrity. Some patients with APS have evidence for antibodies that specifically recognize annexin V and increased levels of these antibodies has also been reported in patients with thrombosis (13).

Although the specific antigenic reactivity of aPL is crucial to their effect, the pathogenic mechanisms that lead to fetal and placental injury *in vivo* are not completely understood. One method of further defining the pathogenesis is to use the antigen binding domain of aPL as a means of localizing the pathogenic antibodies. This domain can activate the complement cascade or bind to Fcγ receptors, or both, and thereby trigger activation of the effectors of injury, leukocytes and platelets (13). Findings from animal models of APS induced pregnancy loss and increased injury-induced thrombosis argue that complement factors C3 and C5 are essential proximal mediators of tissue injury. Intact complement regulation seems to be essential for maintenance of normal pregnancies. In pregnant mice that are deficient in regulators of complement activation, the fetuses die *in utero* surrounded by inflammatory cells and complement split products. However, breeding mice that lack complement inhibitors on a complement-deficient background rescues pregnancies. These studies suggest that uncontrolled activation of the complement pathway leads to pregnancy failure, even without aPL (13). Girardi et al (14) proposed that aPL bind to trophoblasts and exaggerated complement activation overwhelms the inhibitory capacity of local complement regulatory proteins, thereby enabling the complement cascade to proceed. This process leads to recruitment and stimulation of inflammatory cells and injury to the developing fetal–placental unit.

Additionally, their murine models of APS demonstrated that complications of pregnancy are initiated by inflammation rather than by thrombosis. The same group (14) identified a previously unrecognized role for complement as an early effector in pregnancy loss associated with placental inflammation. In a mouse model of APS, complement activation has an essential and causative role in fetal loss and growth restriction. Blockade of the complement cascade *in vivo* with a C3 convertase inhibitor (Crry–Ig), a monoclonal antibody to C5, or a C5a receptor antagonist peptide reverses fetal loss and growth restriction in

pregnant mice that have been treated with human IgG containing aPL. Furthermore, mice deficient in complement C3, C5 or C5a receptors are resistant to fetal injury induced by aPL (15). The different complement components that participate in the pathogenesis of APS are illustrated in Figure 2.

Figure 2. Pathogenic mechanisms of APS

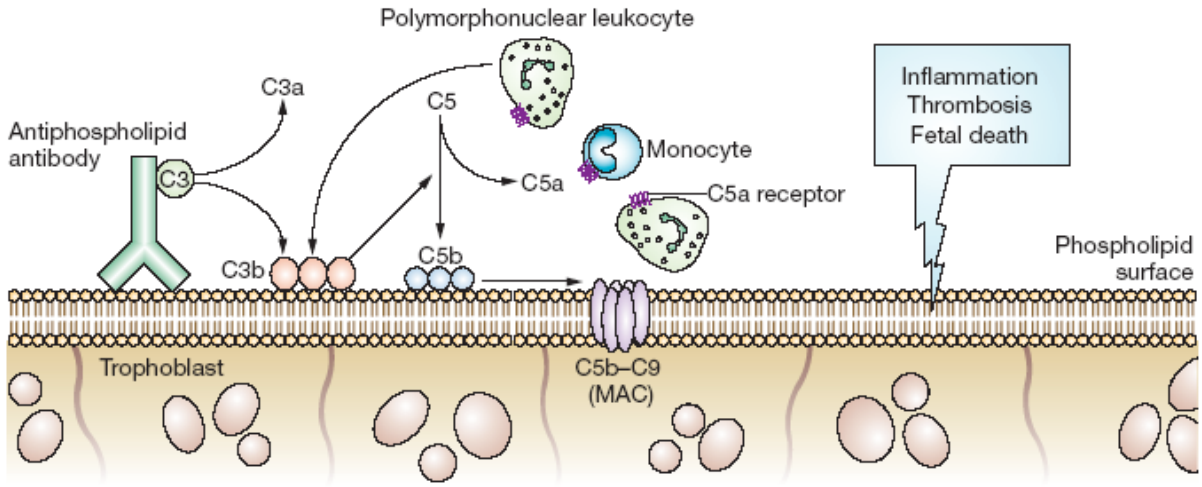


Figure courtesy of Dr J.E. Salmon

4.2 PRIMARY APS

During the early years of the description of APS, the concept of "primary" APS syndrome was accepted as a preliminary step in the evolution of a full blown lupus (16). Currently, it is established that primary APS syndrome is a separate disorder.

In 1988, Ronald Asherson (16) described some particular characteristics in these patients, such as persistent negativity for double stranded DNA antibodies (dsDNA), the presence of ANAs at low titers (between 1:40 and 1:160), and the presence of anti-mitochondrial antibodies which are also directed against phospholipids in mitochondrial membranes. Additionally, he extended the concept of primary APS to 3 groups of patients: 1) patients with idiopathic deep vein thrombosis (DVT), pulmonary embolism (PE) and pulmonary hypertension in the absence of any autoimmune disease, 2) patients with stroke, transient ischemic attacks (TIA) and, less commonly, other large vessel occlusions including myocardial infarction (MI) or peripheral vessel thrombosis, particularly in young patients (under the age of 45) and 3) patients with recurrent fetal losses (16).

Asherson et al (17) performed one of the first multicenter studies in patients with primary APS. Seventy patients were included, 26 (37%) were male, and 44 (63%) female, giving a 2:1 female/male ratio. Mean age was 38 years (range from 21 to 59) and patients were followed for at least 5 years. None of the patients developed SLE during the follow-up. Thirty-eight (54%) of patients had episodes of DVT, being accompanied by PE in 18 cases. Arterial occlusions were found in 31 (44%) patients, mainly in the form of strokes, TIA and MI. Recurrent fetal losses were present in 24 (34%) patients. Other less frequent manifestations were *livedo reticularis* in 14 (20%) patients and avascular necrosis in 2 (3%) patients. ANAs were present in 32 (46%) patients, most of them at low titers (range from 1:10 to 1:160). Only 6 patients had ANAs at high titers (from 1:320 to 1:3200). Antimitochondrial antibodies (M5 type) were present in 11 of 40 patients tested. Sixty patients were positive for LA and aCL, 5

patients had aCL alone and 5 had only LA. Thrombocytopenia was present in 32 (46%) patients and Coombs´positivity was present in 10, accompanied by autoimmune hemolytic anemia in 3 cases. Five out of 70 patients had relatives with SLE, rheumatoid arthritis (RA), or a clotting tendency. The authors suggested that in comparison with APS related with SLE, patients with primary APS have a low incidence of valve lesions, *livedo reticularis*, chorea, fever, myalgia, and arthralgia. The presence of rheumatoid factor (RF), cryoglobulinemia or low complement in a minority of patients might also be indicative of an immune mediated basis in primary APS patients.

Some years later, Piette et al (18) proposed exclusion criteria to distinguish primary and SLE-related APS. The presence of any of these criteria excludes the diagnosis of primary APS: Malar rash, discoid rash, oral or pharyngeal ulceration, frank arthritis, pleuritis in the absence of PE or left-sided heart failure, pericarditis in the absence of MI or uremia, persistent proteinuria greater than 0.5 gram per day, due to biopsy proven immune complex-related glomerulonephritis, lymphopenia (less than 1000 cells), anti dsDNA, antiextractable nuclear antibodies (anti-ENAs), ANAs of more than 1:320, and drugs potential inducers of APS. The authors proposed that a follow-up longer than 5 years after the first clinical manifestation is necessary to rule out the subsequent emergence of SLE.

One of the first studies by Vianna et al (19) compared the different characteristics between primary with SLE-related APS. Fifty-six patients had APS plus SLE and 58 had primary APS. There were no significant differences between the two groups with the exceptions of autoimmune hemolytic anemia (p values: < 0.05), cardiac valve disease (p< 0.005), neutropenia (p< 0.01), and low C4 levels (< 0.001) all of which occurred more frequently in patients with SLE-related APS.

Cervera et al (20) reported the largest survey of APS patients until date. The cohort include 1,000 European patients recruited from 20 different centers. The main clinical features

at disease onset were DVT in 317 (31.7%) patients, thrombocytopenia in 219 (21.9), *livedo reticularis* in 204 (20.4%), stroke in 131 (13.1), superficial thrombophlebitis in 91 (9.1), PE in 90 (9.0), fetal loss in 83 (8.3), TIA in 70 (7.0), hemolytic anemia in 66 (6.6), skin ulcers in 39 (3.9), and epilepsy in 34 (3.4) patients. Eight (0.8%) patients had a CAPS. Cumulative features during evolution of the disease are shown in Table 3.

Of the entire cohort, 53.1% patients had primary APS and 41.2% had APS associated with SLE or lupus-like disease (LLD). Both groups had similar profiles (including age at disease onset), except that patients with APS associated with SLE had more episodes of arthritis (56% versus 3% in patients with primary APS) and *livedo reticularis* (36% versus 16) and more frequently exhibited thrombocytopenia (43% versus 21%) and leukopenia (38% versus 2%). The female/male ratio was higher (7:1) in patients with APS associated with SLE than in patients with primary APS (3.5:1). Patients with childhood-onset APS had more episodes of chorea and jugular vein thrombosis, whereas patients with older-onset APS were more frequently male and had a higher frequency of strokes and angina pectoris, but a lower frequency of *livedo reticularis*, compared with the remaining patients (20).

Soltetsz et al (21) studied a large cohort of 637 Hungarian APS patients. Primary APS was diagnosed in 218 patients and secondary APS in 419 subjects, of whom 288 had SLE. There were significantly more men among the primary compared with the SLE-related APS patients (male: female ratio 39/218 *vs* 27/288). Cerebrovascular thrombosis was significantly more frequent in SLE-related APS than among primary APS patients (128=288 *vs* 77=218). However, there was no difference between the two groups in the occurrence of venous thrombosis, coronary, carotid and peripheral arterial thrombosis, and fetal loss. The frequency of LA, IgM and IgG isotype aCL was similar in the two groups.

Table 3. Cumulative clinical features during the evolution of the disease in 1000 patients with APS

Manifestations	No.	(%)
Peripheral thrombosis		
Deep vein thrombosis	389	38.9
Superficial thrombophlebitis in legs	117	11.7
Arterial thrombosis in legs	43	4.3
Venous thrombosis in arms	34	3.4
Arterial thrombosis in arms	27	2.7
Subclavian vein thrombosis	18	1.8
Neurologic manifestations		
Migraine	202	20.2
Stroke	198	19.8
Transient ischemic attack	111	11.1
Epilepsy	70	7
Multiinfarct dementia	25	2.5
Chorea	13	1.3
Pulmonary manifestations		
Pulmonary embolism	141	14.1
Pulmonary hypertension	22	2.2
Pulmonary microthrombosis	15	1.5
Cardiac manifestations		
Valve thickening/ dysfunction	116	11.6
Myocardial infarction	55	5.5
Angina	27	2.7
Myocardiopathy	29	2.9
Vegetations	27	2.7
Coronary by-pass re-thrombosis	11	1.1
Intraabdominal manifestations		
Renal manifestations	27	2.7
Gastrointestinal *manifestations*	15	1.5
Splenic infarction	11	1.1
Cutaneous manifestations		
Livedo reticularis	241	24.1
Ulcers	55	5.5
Pseudovasculitic lesions	39	3.9
Digital gangrene	33	3.3
Cutaneous necrosis	21	2.1
Osteo-articular manifestations		
Arthralgia	387	38.7
Arthritis	271	27.1
Avascular necrosis of bone	24	2.4
Ophthalmologic manifestations		
Amaurosis fugax	54	5.4
Retinal artery thrombosis	15	1.5
Optic neuropathy	10	1.0
ENT manifestations		
Nasal septum perforation	8	0.8
Hematological manifestations		
Thrombocytopenia (<100 000)	296	29.6
Hemolytic anemia	97	9.7
Obstetric manifestations (pregnant females 590)		
Preeclampsia	56	9.5
Eclampsia	26	4.4
Abruptio placentae	12	2.0
Fetal manifestations (pregnancies 1580)		
Early fetal losses (<10 weeks)	560	35.4
Late fetal losses (>10 weeks)	267	16.9
Live births	753	47.7
Premature births	80/753	10.6

Primary APS is rare in children and little information exists on its potential for evolution into SLE. Gattorno et al (22) reported one of the few series in children. The authors described 14 patients (9 boys and 5 girls), who presented clinical manifestations of APS between 3 and 13 years of age (median 9 years) and were followed for 2 to 16 years (median 6 years). Six patients presented with DVT, 5 with stroke, 2 with peripheral artery occlusion, 1 with Budd–Chiari syndrome and 1 with MI. During follow-up, 4 patients had one or more recurrences of vascular thrombosis. At the last observation, 10 patients could still be classified as having primary APS, 2 had developed SLE (both patients developed anti-dsDNA), 1 LLD and 1 Hodgkin's lymphoma four years after the onset of primary APS. The authors suggested that some children who present with features of primary APS may progress to SLE or LLD.

Espinola-Zavaleta et al (23) studied a series of 24 patients with primary APS prospectively by transesophageal echocardiography (TEE). At baseline, 70% of patients had valve disease, MI was detected in 5 (29%) cases and pulmonary hypertension in 4 (23%). After a 5 year follow-up, a new TEE was performed in 12 patients. Valve lesions were unchanged in 3 patients, and new valve lesions were detected in 3 patients in spite of anticoagulation treatment with acenocumarol.

Environmental and genetic factors contribute to ethnic variation and susceptibility to APS and thus interethnic differences in disease patterns may be due to environmental or genetic factors, or both. The etiology of the APS is linked to genetic predisposition, which may be accounted for, at least in part, by genes of the major histocompatibility complex (MHC) (HLA system). The association between HLA class II genes and aPL production has been reported in a number of studies. The association of HLA-DRB1*04, DRB1*07(0701), DRB1*1302, DR53, DQB1*0301 (DQ7), *0302, and *0303, HLA-DR4, -DR7, DR5, -DRw53, DRB10901, DPB11501,DPB1-2301, HLA-DPB10301, DPB11901, and DQB106, with aCL has been demonstrated in APS (24).

Goldstein et al (25) studied 91 SLE and 16 primary APS Caucasian patients from Ottawa, Canada. aPL were found in 19 (21%) of 91 SLE patients. HLA-DR17 and Dw24 were decreased in patients with SLE with aPL and in patients with APS. HLA-DR4 and the linked DR53 were significantly increased in patients with primary APS compared to patients with SLE. In patients with aPL (SLE and primary APS) compared to patients with SLE without aPL, associations were found with HLA-DR53, DR7 and to a lesser degree with DQ7. Freitas et al (26) performed a genetic analysis of the MHC profile of 34 Brazilian patients with primary APS and 35 secondary APS (related to SLE). Compared with controls, patients with primary APS exhibited a non-significantly increased frequency of DR53 associated alleles, and patients with secondary APS presented an increased frequency of HLA-DRB1*03 alleles. A trend towards an increase in the frequency of the DQB1*0604 allele and of the DQB1*0302 allele was seen in secondary APS. Caliz et at (27) studied 83 British Caucasian patients with APS (53 with primary APS and 30 with APS associated with SLE). The authors found a number of possible HLA alleles and haplotypes associated with APS. The major association seen was between the DQB1*0604/5/6/7/9-DQA1* 0102-DRB1*1302 haplotype and APS. The frequency of this haplotype was greater in primary APS than in secondary APS, with the association being even stronger in anti β_2GPI positive primary APS.

Despite the heterogeneity in the clinical expression of APS, some clinical features that can be grouped in different clusters. Krause et al (28) analyzed 246 patients with APS and after clinical stratification and statistical analysis (by factor analysis) found different clusters for APS. The first group of patients is characterized by cardiac valves abnormalities, *livedo reticularis* and neurologic manifestations (epilepsy and migraine). The second group represents the association between arthritis, thrombocytopenia and leukopenia. The third group represents the association between recurrent fetal loss and intrauterine growth restriction and the fourth group constitutes the inverse correlation between arterial and venous thrombosis.

The authors suggested that once any of these features or lesions is recognized in a specific APS patient, special attention should be paid to for the future emergence of the other cluster manifestations.

4.3. APS ASSOCIATED WITH OTHER DISEASES

APS was first recognized in patients with SLE and was then found a lower frequency in patients with other autoimmune disorders. Additionally, aPL (either aCL or LA) are occasionally elevated in normal individuals or can be present in a series of chronic conditions such as infectious diseases, neoplasms or can be induced by drugs.

In a study of 552 randomly selected healthy blood donors, IgG aCL were present in up to 9.4 percent in a first test and were persistent in approximately 1.4 percent (29). Increased levels of IgG or IgM aCL have been observed in 12 to 52 percent of the elderly. The prevalence of the LA has ranged from 1.7 percent of patients with suspected venous thromboembolism who did not have the disease to 8 percent in healthy blood donors (30). aPL also occur with increased frequency (10-15 percent) in women with more than three spontaneous recurrent abortions (31).

Both LA and aCL have also been found in patients with a variety of autoimmune and rheumatic diseases (32-34) including: hemolytic anemia, idiopathic thrombocytopenic purpura (ITP) (up to 30 percent) (35), juvenile arthritis (28-46%) (36), RA (7 to 50 percent) (37), psoriatic arthritis (28 percent) (38), systemic sclerosis (SSc) (25 percent), especially with severe disease (39), Behcet's syndrome (7-20 percent) (40), primary Sjögren's syndrome (pSS) (25 to 42 percent) (41, 42), mixed connective tissue disease (22 percent) (43), polymyositis and dermatomyositis (44), polymyalgia rheumatica (20 percent) (45), chronic discoid lupus erythematosus (46), eosinophilia myalgia and toxic oil syndrome (47), vasculitis (48) and autoimmune thyroid disease (43 percent) (49) among others.

Several drugs have been implicated as potential inducers of APS, including phenothiazines (chlorpromazine), phenytoin, hydralazine, procainamide, quinidine, quinine, dilantin, ethosuximide, alpha interferon, amoxicillin, chlorothiazide, oral contraceptives, and propranolol (50,51).

4.3.1 APS ASSOCIATED WITH SLE

Reports of the prevalence of aPL in SLE are myriad and have varied widely, depending on the antigen source and method used. The prevalence of LA has been estimated at10 to 30% of patients and aCL at 18 to 86% of patients (52,53).

Cross-sectional studies of aPL in SLE underestimate the true prevalence, because many SLE patients make these antibodies intermittently. In fact, some SLE patients make aPL only after thrombotic events, demonstrating the importance of prospective studies in SLE.

Previous estimates have suggested that 30% of SLE patients will develop APS [52,54]. In the Hopkins Lupus Cohort, after at 20 years of follow-up, there was a 50% chance of having an arterial or venous thrombotic event if the SLE patient had LA (53). Conversely, aPL may precede full blown SLE by several years. McClain et al (55) analyzed prediagnosis serum samples of 130 individuals who had been diagnosed with SLE. aPL measured by aCL IgG and/or IgM were detected in 18% of the SLE patients prior to diagnosis. aCL appeared from 7.6 years prior to SLE diagnosis to within the same months as SLE diagnosis, with a mean onset of 3 years before SLE diagnosis. Additionally, the presence of aCL predicts a more severe clinical outcome; these patients had more frequent renal disease, CNS involvement, thrombocytopenia and clotting events.

The presence of aPL is a poor prognostic factor in critically ill SLE patients. Williams et al (56) reported 61 SLE and APS patients who required intensive care unit (ICU) admission. A diagnosis of APS was made in 37 (61%) of the 61 patients; 36 with coexisting SLE and one with primary APS. aPL tests were positive in 32. APS patients had an increased rate of ICU death and reduced long term survival.

Cervera et al (57) assessed the main causes of morbidity and mortality in a cohort of 1000 European patients suffering from SLE during a 10-year period. Thromboses were a predominant cause of death in 18 patients and were always associated with the presence of

aPL. The most common thrombotic events were cerebrovascular accidents (11.8%), coronary occlusions (7.4%), and PE (5.9%). When the causes of death during the initial 5 years of follow-up were compared with those during the ensuing 5 years, active SLE and infections (28.9% each) appeared to be the most common causes during the initial 5 years, while thromboses (26.1%) were the most common cause of death during the last 5 years.

The presence of aPL may condition the clinical setting of SLE in different organs, such as the heart, CNS, kidneys and lungs, among others. It has been shown that the prevalence of valvular abnormalities, particularly left sided valve lesions, is higher in SLE patients with aPL than in those without. Khamashta et al (58) showed that patients with SLE and aPL have an increased frequency of mitral valve vegetations and mitral regurgitation than aPL-negative patients (16 vs 1.2% and 38 vs 12%, respectively). In this study, 9 of 50 patients with mitral valve disease had cerebrovascular occlusions during follow-up, showing that valvular lesions can be a source for emboli and a possible cause of ischemic stroke in aPL patients, as reported by other authors. In patients with SLE, particularly women between 35 and 44 years of age, the risk of cardiovascular events is over 10 times higher than in healthy women of similar age (59).

Early studies by Mackworth-Young and Hughes in 1985 (60) found a higher prevalence of aPL in SLE patients with seizures, higher than the accepted prevalence in the common SLE population. Herranz et al (61) confirmed that in SLE patients, moderate-to-high titers of IgG aCL are associated with seizures, suggesting a role in the etiopathogenesis of epilepsy in SLE. These authors found a statistically significant higher prevalence of aPL in SLE patients with seizures compared with control SLE patients. The titer and isotype of aCL were important in determining the presence of clinical complications. Moderate-to-high titers of IgG aCL were the most strongly implicated in relation to the appearance of seizures, while the IgM isotype appeared to be less specific. These findings provided evidence against a casual

association and suggested that the IgG isotype of aCL may have a pathogenic role in SLE-associated epilepsy.

Cognitive dysfunction varies from global dysfunction in the context of multi-infarct dementia to subtle cognitive deficits in otherwise asymptomatic patients with aPL. Denburg et al. (62) evaluated the relationship between aPL positivity (expressed as LA) and cognitive dysfunction in patients with SLE in a cross-sectional study. LA-positive patients were 2 to 3 times more likely than LA-negative patients to be designated as cognitively impaired by the application of specific psychometric tests, with lower performance on tasks of verbal memory, cognitive flexibility and psychomotor speed. These deficits occurred independently of clinically overt neuropsychiatric manifestations. The authors speculated that LA positivity is associated with subclinical nervous system compromise, possibly on the basis of ongoing LA-related microthrombotic events or vasculopathy.

Recently, we described the clinical and radiological characteristics of 30 patients with dementia associated with APS (63). There were 21 female patients and the mean age of patients was 49 years (range 16–79 yr). Fourteen (47%) of the patients suffered from primary APS, 9 (30%) had SLE and 7 (23%) patients had LLD. The main neurologic features included cerebrovascular accidents in 11 (37%) patients, migraine in 7 (23%), seizures in 4 (13%), TIA in 2 (7%), chorea in 2 (7%), and retinal thrombosis in 2 (7%) patients. Other APS-related manifestations included thrombocytopenia in 12 (40%) patients, heart valve lesions in 8 (27%) and DVT in 7 (28%) patients. Cortical infarcts were found in 19 (63%) patients, subcortical infarcts in 9 (30%), basal ganglia infarcts in 7 (23%) and signs of cerebral atrophy in 11 (37%). Although 63% of patients had APS manifestations before the diagnosis of dementia, only a minority (37%) were receiving anticoagulation. The mean time evolution from initial manifestation of APS to the diagnosis of dementia in these patients was 3.5 years.

Although the outcome of renal transplant in patients with SLE does not differ from that of other populations, the presence of aPL modifies their prognosis. A number of studies have reported a poor outcome, with high rates of graft loss as a result of thrombotic events in patients with SLE positive for aPL (64-66). Fernandez-Fernedo et al (67) demonstrated that patients who developed postransplant aPL *de novo* showed a higher rate of acute rejection. In addition, in patients who suffered any episode of acute rejection, the production of postransplant aPL was associated with a higher frequency of postransplant cardiovascular disease.

The prevalence of pulmonary hypertension in APS associated with SLE and primary APS has been estimated to be between 1.8% and 3.5%, respectively (68). In a prospective analysis of 500 patients with SLE, a statistically significant association between pulmonary hypertension and the presence of IgA aCL above 2SD has been described (69). Other pulmonary complications related to APS in SLE patients include pulmonary hemorrhage, adult respiratory distress syndrome (ARDS) and pulmonary microthrombosis (68).

Not every positive aPL test is diagnostically and clinically significant in SLE patients. Interpretation of a significantly positive aPL test in SLE patients should take into account the following rules: Transient aPL positivity is common in the general population, especially during infections, and thus documentation of persistence (at least 12 weeks apart) of autoimmune aPL is crucial; a positive LA test is a more specific but less sensitive predictor of aPL-related events than is aCL; moderate to high titers aCL IgG/M (> 40 U) and/or β_2GPI IgG/IgM antibodies are more strongly associated with aPL-related clinical events than are low titers; and multiple positive aPL tests yield a worse prognosis than does any single type of test (70).

4.3.2 APS ASSOCIATED WITH INFECTIONS

Since 1983, many infections have been found to be associated with aPL positivity, although the pathogenic role of these antibodies was not usually obvious except in a few isolated cases. Recently, there have been various reports that many infections may not only trigger the production of these antibodies but also appear to be accompanied by clinical manifestations of APS itself. This has been seen particularly in patients with CAPS. Some authors have proposed that infections may be a trigger for the induction of pathogenic aPL in certain predisposed subjects. The β_2GPI induced by infections may bind to "self" aPL thus forming an immunogenic complex against which aPL are then produced. What constitutes this predisposition is unknown at this time, but clearly genetic factors might have a significant role. The antibodies produced by infectious triggers are therefore heterogeneous in their dependency on β_2GPI, and a minority may resemble the "autoimmune" type (71).

Viruses and microbial agents may induce autoimmune disease by several differing mechanisms. The mechanism which concerns the production of aPL and indeed the APS is known as molecular mimicry. A hexapeptide, TLRVYK recognized specifically by a pathogenic anti- β_2GPI monoclonal antibody was recently identified by Blank et al (72*)*. They evaluated the pathogenic potential of microbial pathogens carrying sequences related to this hexapeptide in mice by infusing intravenously into naïve mice IgG specific to the peptide. High titers of antipeptide anti-β2GPI antibodies were seen in mice immunized with *Haemophilus influenzae*, *Neisseria gonorrhea*, and tetanus toxoid. Significant thrombocytopenia, prolonged activated partial thromboplastin times, and increased fetal loss were seen. Thus, it is apparent that experimental APS can be induced by immunization with certain microbial pathogens which share epitope homology with the β2GPI molecule (72).

We recently described the clinical and serological characteristics of 100 patients with APS related with infections (73). Fifty nine per cent were female and 41% male. Their mean

(SD) age was 32 (18) years (range 1 to 78). There were 24 young patients (under 18 years), who were affected mainly by skin and respiratory infections. Sixty eight patients had primary APS, 27 had SLE, two had LLD, two had inflammatory bowel disease (one Crohn's disease and one ulcerative colitis), and one had RA. In 40 of the 100 cases, the thrombotic events appeared in the form of CAPS.

The main clinical manifestations of APS included: pulmonary involvement (39%), skin involvement (36%), and renal involvement [35%; nine with renal thrombotic microangiopathy (TMA)]. The main associated infections and agents included skin infection (18%), HIV (17%), pneumonia (14%), hepatitis C (HCV)(13%), and urinary tract infection (10%), upper respiratory infections (9%), sepsis (6%) and gastrointestinal infections (6%) among others.

Uthman and Gharavi reviewed the relationship between viral infections and the induction of aPL (74). aCL antibodies were frequently found in patients with chronic HCV infection and were seen in 22% to 44% of these patients. The clinical significance of these antibodies is controversial. Although most investigators suggest that these antibodies are not pathogenic, thrombotic events such as renal TMA and lacunar brain infarction have been reported (74).

Ramos-Casals et al (75) collected 82 patients with chronic viral infections associated with APS (45 with chronic HCV, 32 with HIV infection and 5 with HCV-HIV coinfection). The main features of APS were avascular bone necrosis in 20 patients, peripheral thrombosis in 17, thrombocytopenia in 15, neurologic features in 13, cardiac manifestations in 12, PE in 9, gastrointestinal manifestations in 8, and cutaneous manifestations in 8 patients. The main APS-related features in HCV-infected patients were intraabdominal thrombosis and myocardial infarction, whereas, in HIV-infected patients, the main features were avascular bone and cutaneous necrosis. The authors proposed that chronic viral infections such as HCV and HIV,

might act, in some patients, as chronic triggering agents that induce a heterogeneous, atypical presentation of APS.

aCL have been frequently reported in patients with HIV infection. The antibodies were predominantly of the IgG isotype and were seen in up to 94% of these patients. Similarly to HCV, the clinical significance of these antibodies in HIV infection is controversial. Although most studies, in addition to investigations on the nature of the target epitope for HIV-induced aPL, have shown that these antibodies are not pathogenic and do not appear to be of the autoimmune type, thrombotic events such as recurrent TIA, stroke, splenic infarction, and necrotic skin lesions have been reported (74). Galrao et al (76) studied the prevalence of aCL and anti β_2GPI antibodies in 90 Brazilian patients infected by HIV, of whom 40 (44.4%) were reactive for at least one type of aPL (aCL and/or anti-β2 GPI). The frequency of aCL was 17.8%, of which 15 (17%) had aCL IgG, 3 (3%) IgM, and 1 (1%) IgA. Clinical manifestations of APS were detected in 12 patients (13%) of the studied population, 7 patients (8%) had at least one thrombotic complication, and 7 patients (8%) had at least one obstetric complication. There was no statistically significant association between the presence of these manifestations and the presence of at least one of the aPL tested.

We documented the case of a 35-year-old African woman with HIV infection and SLE who developed recurrent episodes of DVT and PE in the presence of antiprothrombin (anti-PT) antibodies (77). Our case is most unusual in that, during the first years, the only autoantibodies to phospholipid detected were those against prothrombin. Recently, there has been much interest in the detection of anti-PT as a further means of detecting aPL, which might be useful in patients who had previously been found to be aPL negative by means of repeated testing with conventional methods.

Several other viral infections had been related with APS including cytomegalovirus, varicella zoster virus, Epstein-Barr virus, adenovirus and Parvovirus B19 among others (74).

It is also well known that infections are common triggers of CAPS. The CAPS Registry, shows that at least 60% of patients appear to have developed CAPS following an identifiable trigger factor, with infections dominating the list. These include non-specific viral infections, pneumonia, infected leg ulcers, upper respiratory, urinary, gastrointestinal and cutaneous infections, as well as specific infections such as typhoid fever, malaria and Dengue fever, among others (79).

4.3.3 APS ASSOCIATED WITH VASCULITIS

aPL and thrombosis may also occur in patients with primary systemic vasculitis (PSV). Several case reports have described APS in individual patients with polyarteritis nodosa (80), microscopic polyangiitis (81), and, in particular, Wegener's granulomatosis (82). Other reports described several patients with giant cell arteritis/polymyalgia rheumatica (83) and APS or Behçet's disease and APS (84). In the European cohort of 1000 consecutive patients with APS only a very small proportion (0.7%) of patients had a diagnosis of systemic vasculitis (20). There are a limited number of published series of patients with PSV and APS.

We recently reported the prevalence of aPL in a cohort of patients suffering from PSV in a single center (48). One hundred and forty four patients (53 male, 91 female) were included with a median age of 54 years (range 18–91). Of the 144 patients, 89 were classified according to the ACR criteria and a further patient was diagnosed with microscopic polyangiitis according to the Chapel Hill Consensus definition. Patients classified according to the ACR criteria included: 42 with Wegener's granulomatosis, 18 Churg-Strauss syndrome, 14 polyarteritis nodosa, 6 Henoch-Schönlein purpura, 6 giant cell arteritis, and 3 Takayasu's arteritis. Eighteen were classified clinically as follows: cutaneous vasculitis (9 patients), vasculitis of the central nervous system (3 patients), mesenteric vasculitis (2 patients), cryoglobulinemic vasculitis (2 patients), relapsing polychondritis (1 patient), and retinal vasculitis (1 patient). A further 36 patients with vasculitis remained unclassified.

Of these 144 patients, 25 (17%) had some features of APS: 9 (6%) had classical APS according to the Sapporo criteria while 4 had features of APS with positive serology but not sufficient for the Sapporo criteria (probable or possible APS). A further 12 patients had positive aPL serology with no significant clinical features; the remaining 119 patients were completely negative for aPL. Of the 12 patients with positive aPL but without clinical features of APS, one had positive serology for both aCL and LA, four were positive for aCL alone, and

the remaining seven were LA positive. Of the seven positive for LA alone, four were positive on multiple occasions.

We found a prevalence of definite APS of 6% (9/144) in our population of patients with PSV. A further 3% (4/144) had features (both clinical and serological) of APS and were classified as possible APS. Additionally, 8% (12/144) had positive serology for aCL or LA, or both. Our series of patients highlight the fact that some patients appear to have highly pathogenic LA or aCL and thrombosis while other patients, often with high antibody titers, do not. It is possible that the pathogenicity of the antibodies is influenced by host genetic factors, antibody isotype, and underlying vessel wall integrity.

4.3.4 APS ASSOCIATED WITH MALIGNANCIES

Since the discovery of aCL, there have been many isolated case reports of the association of aCL with vascular events in patients with a variety of malignant conditions including solid tumors, and lymphoproliferative and hematological malignancies. It is now clear that aPL should always be considered in the pathogenesis of vascular occlusion occurring in patients demonstrating Trousseau's syndrome (85) .

Several mechanisms have been suggested for the association between aPL and cancer and include the following: (1) production of autoantibodies by the immune system as a response to tumor antigens; (2) production of monoclonal immunoglobulins with LA and aCL activities; and (3) secretion of aCL from tumor cells (85).

Some studies have focused on the association between aPL and solid and hematological malignancies but with limited information on their clinical (thrombotic) presentation. A large prospective epidemiological study on the occurrence of malignant disease in aPL-positive patients was conducted in Montpelier, France in 1994 (86). One thousand and fourteen patients were tested at entry and, interestingly carcinoma was the most frequently associated disease. Of the 72 aPL positive patients, 14 had a history of carcinoma, nine had active malignant disease while five were in clinical remission. The main related malignancies found were prostatic adenocarcinoma, breast carcinoma, ovarian carcinoma and colon adenocarcinoma.

Zuckerman et al (87) studied the prevalence of aCL in patients with malignancy and the possible association of aCL with thromboembolic events. They included 216 patients in their group and an age-matched control group of 88 healthy subjects. Forty-seven (22%) of the cancer patients were found to be aCL-positive compared with only three (3%) of the control group. The aCL-positive cancer patients had a significantly higher rate of thromboembolic events than aCL-negative cancer patients (13/47=28%) *vs*. (24/169=14%) respectively ($P<0.05$).

Miesbach et al (88) retrospectively studied the thrombotic manifestations in 58 patients demonstrating aPL and a history of neoplasia. Thirty-nine patients (67%) suffered from solid tumors such as tumors of the breast in 9 patients, prostate in 4, urinary tract in 4, colon in 4, brain in 3, thyroid in 3, larynx in 3, kidney in 2, cervix in 2, skin in 2, tonsils in 1, cutaneous squamous cell carcinoma in 1, parotid in 1, testicle in 1 and liver tumor in 1 patient. Nineteen patients (33%) had hematological or lymphoproliferative malignancies, including non-Hodgkin's lymphoma in 9 patients, myeloproliferative disease in 5 patients, acute leukemia in 2 patients, Waldenström's macroglobulinemia in 2 patients and monoclonal gammopathy in 1 patient. Four patients suffered from a combination of malignancies such as carcinoma of the breast and hypophysis, carcinoma of the breast and melanoma, carcinoma of the kidney and testis, malignant lymphoma with a carcinoma of prostate and testis.

Of the 58 patients, 46% had positive LA, 41% had elevated IgG aCL, 64% had elevated IgM aCL titers and 55% had elevated levels of both. Of the patients with solid tumors, 18/39 (46%) patients had thromboembolic complications of the APS. Of the patients with hematologic and lymphoproliferative malignancies, only 6/19 (32%) suffered from thromboembolic complications. There was, however, no relation between the titers of aCL antibodies and the clinical manifestations. Finally, the authors suggested that the presence, but not the titers, of aPL may identify a subset of cancer patients with a high risk of developing thrombotic complications (88).

4.3.5 APS ASSOCIATED WITH OTHER AUTOIMMUNE DISEASES AND DRUGS

Recent reports have confirmed increased concentrations of aPL in patients with RA, pSS or SSc, resulting in some cases in a increased risk for thrombosis or related APS manifestations such as thrombocytopenia or hemolytic anemia.

The frequency of aCL in RA patients ranges from 12 to 48% in different series (89-92). aCL have been correlated in patients with RA with high levels of C-reactive protein, and repeated miscarriages (89), RF and ANAs (89, 90), extra-articular manifestations (90), nodules (91) and hemolytic anemia (92).

Bonnet et al (93) studied 50 consecutive patients (36 women, 14 men) with RA and assessed the presence of aCL and anti $ß_2$GPI antibodies by ELISA. Nine patients (18%) had low titer IgG isotype aCL, but no anti $ß_2$GPI antibodies. There was no correlation with thrombosis or recurrent fetal loss. There was a non significant increase in sicca syndrome and extra-articular manifestations of RA in the aCL positive group. No significant association was found between aCL and other autoantibodies (RF, ANA, antikeratin antibodies). No statistically significant association was found between any drug inducing aCL and the presence of aCL.

aCL have been linked to a higher risk of developing atherosclerosis in patients with RA. Pahor et al (94) evaluated internal carotid artery intima-media thickness and the presence of aPL in a selected group of 70 patients with RA (premenopausal women, non-diabetic, non-hypertensive) and compared them with age-sex matched controls. There was a significantly higher internal carotid artery intima-media thickness and number of plaques in RA patients compared to controls. IgG and IgM aCL were present in 15.7% of RA patients compared with 5% in the control group, whilst anti- β_2GPI were positive in 30% of RA patients compared with 7.5% in controls.

Sherer et al (95) studied the prevalence of aCL and anti oxidized low density lipoprotein (anti-oxLDL) in 82 patients with RA. Elevated levels of IgG aCL were detected in 17 of 82 (21%) RA patients, including 10 with low levels of IgG aCL and 7 with medium to high levels of aCL. IgM aCL was found in only 1 (1%) patient, and both IgG and IgM anti-β_2GPI were found in 3 (4%) patients with RA. Elevated levels of anti-oxLDL antibodies were found in 8 (10%) patients, 4 of whom also had elevated levels of IgG aCL.

Seriolo et al (96) evaluated the presence of aPL and plasma levels of protein S in 184 patients with RA and extra-articular involvement. Of the 184 patients, 35 (19%) presented with at least one type of aPL. LA was present in 7 patients with concomitant aCL positivity. The prevalence of aCL isotypes was as follows: IgG isotype was found in 22 cases, IgM in 8 cases and both in 5 cases. Thrombotic events were diagnosed in 34% of aCL-positive patients with RA (12/35, 7 venous and 5 arterial thrombosis). Low free protein S levels were found in 22 of 184 RA patients. Eleven of these 22 RA patients with low free protein S levels were positive for aCL. RA patients with positive aCL and a history of arterial and/or venous thromboses showed lower levels of free protein S compared with patients with positive aCL but no history of thrombosis.

Tumor necrosis factor (TNF)-α inhibitors (adalimumab, etanercept, infliximab) have proven to be highly effective in the treatment of RA; they reduce disease activity and delay radiographic progression, with quite a good safety profile. Side effects of anti-TNF-α treatment include an increased risk for infection and induction of autoantibodies such as ANA, anti-dsDNA and aCL. One possible explanation for the induction of aCL positivity in patients treated with anti-TNF-α is that down-regulation of TNF- α leads to up-regulation of IL-10, which in turn activates autoreative B cells and thus induces autoantibody production (97).
Ferraccioli et al (98) studied the induction of aCL in 8 RA patients treated with etanercept and followed during 85 weeks. Five patients presented an increased of aCL IgG levels, while anti-

DNA became positive in 3/8 patients. The authors have showed that the appearance of these autoantibodies correlated with bacterial urinary infection or upper respiratory tract infections, and that antibiotic treatment restored normal aCL antibody levels.

Bobbio-Pallavicin et al (99) studied 39 RA patients treated with Infliximab followed during 78 weeks and found a significant increase in aCL titers, starting at 30 weeks for IgM antibodies and at 78 weeks for IgG antibodies. However, in most cases the levels did not exceed normal limits, even after 78 weeks, and none of the patients exhibited any clinical feature related to APS.

Several authors have studied the prevalence of aPL in patients with pSS. The frequency of aPL in pSS patients has ranges from 14 to 34% (41, 42, 100-103). Cervera et al (100) studied the prevalence of aPL in 80 patients with pSS. Only 11 (14%) patients were found to have aPL (aCL, LA or both) in their sera, but anti β_2GPI were not detected in any patient. None of the patients with pSS was diagnosed with APS. Fauchias et al (104) studied 74 French patients with pSS. aPL were found in 25 (34%) patients; IgG in 23 (12 had low titers, 6 moderate titers and 5 high titers) and IgM in 5 (3 and 2 had moderate and high titers, respectively). Eight (11%) patients had LA; anti-ß$_2$GPI were detected only in 3 (4%) patients. Only 2 patients with LA, aPL and β_2GPI had recurrent venous thrombosis.

Recently, Ramos-Casals et al (42) described 82 patients with pSS and atypical autoantibodies from a total cohort of 402 patients with pSS. Thirty-six patients had aPL: aCL were found in 24 patients, IgG in 19 (8 had low positive levels, 6 had moderate positive levels, and 5 had high positive levels), IgM in 6 (4 had low positive levels and 2 had high positive levels) and LA in 19 patients. Four (11%) of the 35 pSS-aPL patients fulfilled the current classification criteria for APS. Two additional patients had probable APS, with thrombosis but with only 1 positive aPL determination. The authors reviewed reported cases with pSS and found 134 patients reported as having aPL. Based on collected data, the authors noted some

particular characteristics in pSS patients with APS including the infrequent detection of IgM-aCL and the low prevalence of an associated APS (3%).

The prevalence of aPL in SSc has been reported at 0 and 41%, and most studies have focused on aCL (39,104,105). Parodi et al (104) studied 90 patients with SSc (86 females) who were tested for IgG and IgM aPL by ELISA in which the wells were coated with a mixture of cardiolipin, phosphatidyl serine, phosphatidyl inositol and phosphatidic acid, plus β_2GPI as cofactor. Fourteen patients proved to have antibodies directed at a mixture of phospholipids. Eleven patients (12%) had antibodies to a single phospholipid or to a combination of different phospholipids. Two of them had diffuse SSc and 9 the limited form of SSc. All aPL-positive patients had IgG aCL, 3 had anti-phosphatidyl serine, 2 anti-phosphatidyl inositol and 2 anti-phosphatidic acid antibodies. Three had β_2GPI antibodies alone.

Sanna et al (105) determined the prevalence and clinical significance of aCL, anti β_2GPI and antibodies to phosphatidylserine-prothrombin complex (aPS-PT) in 25 patients with SSc (18 with limited and 7 with diffuse SSc). aPL were present in 8/25 patients. IgG and IgM aCL were more frequently found in patients with SSc than in controls (24% vs 5% and 16 vs 3%, respectively). The prevalence of anti β_2GPI did not differ between patients and controls. Patients with telangiectasia and pulmonary hypertension had IgM aPS-PT more frequently than those without (37.5 vs 0%, and 66 vs 4.5%, respectively). No associations were found between the other aPL analyzed and clinical manifestations of SSc. One patient with SSc who had had venous thrombosis also had IgG aCL at low titers.

4.4 CATASTROPHIC APS

The ‘‘catastrophic’’ variant of APS is an accelerated form of this syndrome resulting in multiorgan failure due to of multiple small vessel occlusions. Since the early description in 1992 by Asherson (8) more than 300 cases have been collected in the CAPS Registry (an international registry of patients with CAPS created in 2000 by the *European Forum on Antiphospholipid Antibodies*, www.med.ub.es/MIMMUN/FORUM/CAPS.HTM). Patients with CAPS have in common: a) clinical evidence of multiple organ involvement developing over a very short period of time; b) histopathological evidence of multiple small vessel occlusions, and c) laboratory confirmation of the presence of aPL, usually in high titers. Furthermore, approximately 60% of catastrophic episodes are preceded by a precipitating event, mainly infections, trauma or surgical procedures, anticoagulation withdrawal, lupus flares, malignancies or during pregnancy and the puerperium (106-107)

The heterogeneity of the different clinical forms of presentation led to the development of consensus criteria for the definition and classification of these patients. In September 2002, a pre-symposium workshop held during the “Tenth International Congress on aPL” in Taormina, Sicily, Italy, established preliminary criteria for the classification of the CAPS (Table 4) and were recently published (108) and validated (109).

From the analysis of the initial 176 patients included in the CAPS Registry (10), 89 (51%) of the previously included patients with CAPS were classified as having “definite” and 70 (40%) as “probable” CAPS. The sensitivity of the criteria was 90.3% and the specificity 99.4%. Positive and negative predictive values were 99.4% and 91.1%, respectively (109). Patients may develop CAPS *de novo*, without any previous history of thrombosis either associated with a primary APS or SLE. However, it has been shown that previous DVT, fetal loss or thrombocytopenia are the most frequently encountered preexisting aPL associated manifestations.

Table 4. Preliminary criteria for the classification of CAPS.

Evidence of involvement of three or more organs, systems and/or tissues*
Development of manifestations simultaneously or in less than a week.
Confirmation by histopathology of small vessel occlusion in at least one organ or tissue**.
Laboratory confirmation of the presence of antiphospholipid antibodies (LA and/or aCL)***

* Usually, clinical evidence of vessel occlusions, confirmed by imaging techniques when appropriate. Renal involvement is defined by a 50 % rise in serum creatinine, severe systemic hypertension (>180/100 mm Hg) and/or proteinuria (>500 mg/24 hours).

** For histopathological confirmation, significant evidence of thrombosis must be present, although vasculitis may coexist occasionally.

*** If the patient had not been previously diagnosed as having APS, laboratory confirmation requires that aPL must be detected on two or more occasions at least 6 weeks apart (not necessarily at the time of the event), according to the proposed preliminary criteria for the classification of definite APS (9).

Definite CAPS:

- All 4 criteria

Probable CAPS:

- All 4 criteria, except for involvement of only two organs, systems and/or tissues.
- All 4 criteria, except for the absence of laboratory confirmation at least 6 weeks apart due to the early death of a patient never previously tested for aPL prior to the CAPS event.
- 1, 2 and 4
- 1, 3 and 4 and the development of a third event in more than a week but less than a month, despite anticoagulation.

The clinical manifestations of CAPS depend mainly on two factors: a) organs affected by the thrombotic event and the extent of the thrombosis, and b) manifestations of the systemic inflammatory response syndrome, which are presumed to be due to excessive cytokine release from affected and necrotic tissues. There are thus two separate distinct sets of manifestations, each of which requires effective therapy (110).

The main clinical features are intraabdominal thromboses affecting the kidneys (70%), intestine and mesentery (24%), spleen (19%), adrenal glands (13%), or pancreas (7%). Pulmonary complications are next in frequency, with ARDS (111) and PE accounting for the majority, while pulmonary hemorrhage, microthrombi, pulmonary edema and infiltrates occur in a minority of patients.

The CNS is affected in the form of infarcts, encephalopathy, seizures or cerebral venous occlusions. Cardiac problems occur in 53%, with valve defects (mitral, aortic) often present. MI are a presenting feature in 25% of cases. Additionally, other organs may be occasionally affected, including testicular/ovarian infarction, necrosis of the prostate, acalculous cholecystitis, bone marrow infarction, esophageal rupture, giant gastric ulceration, colonic ulcerations, etc (110).

Among laboratory features, thrombocytopenia is present in 60% of cases. One third have evidence of hemolysis, 13% have disseminated intravascular coagulation (DIC) (113) and 8% of patients have thrombotic microangiopathic hemolytic anemia (110). aCL are usually positive with IgM being less frequent. Patients with SLE demonstrate positive ANAs, anti dsDNA and to anti-ENA.

Unfortunately, at present, despite the proposed therapies, the mortality is extremely high (around 50%). The combination of high doses of iv heparin, iv steroids plus repeated doses of iv gammaglobulins and/or plasma exchange is the treatment of choice. In a recent analysis of the CAPS Registry focused on mortality (113), the major cause of death was

identified in 81/114 (71.1%) patients. Cerebral involvement was the most frequent cause of death, in 22 (27.2%) patients and included stroke in 15 (18%), cerebral hemorrhage in 4 (5%), and encephalopathy in 3 (3.7%) patients. Cardiac involvement was identified in 16 (19.8%) patients as the major cause of death, including cardiac failure in 14 (17%) and arrhythmias in 2 (2 %) patients. Infection was described as the main cause of death in 20% of the cases and pulmonary involvement in 10% (due to ARDS, PE or pulmonary hemorrhage) (113).

Recently, Bayraktar et al (114) compared the demographic, clinical, and laboratory characteristics of 127 patients with CAPS associated with primary APS (primary-CAPS) with 103 patients with CAPS associated with SLE (SLE-CAPS). The incidence of organ system involvement was similar in the two groups except any cerebral and pancreatic involvement, which were more common in patients with SLE-CAPS. No differences in the aPL profile were found between the 2 groups except for a higher prevalence of high tites (≥ 80 U) of IgG aCL in patients with primary-CAPS. Logistic analysis showed that renal involvement, anticoagulation, cyclophosphamide, and hemodialysis had a significant effect on the prognosis in patients with primary-CAPS, while any pulmonary involvement, thrombocytopenia, anticoagulation, and cyclophosphamide had significant effect on the prognosis in patients with SLE-CAPS. The authors suggested that SLE is a poor prognostic factor in patients with CAPS.

Patients with CAPS who recover, usually have a stable course with continued anticoagulation. Erkan et al (115) found that 66% of patients with CAPS who survived the initial event had remained symptom-free for an average follow-up of 62.7 months. Fortunately, relapses are infrequent in CAPS patients, being reported in 9 out of 282 (3.2%) patients with CAPS. Of a total 18 episodes analyzed, a precipitating factor was identified in half (mainly infections). Laboratory features of microangiopathic hemolytic anemia were present in 13/18 (72%) episodes (unpublished data).

In conclusion, CAPS is a potentially life-threatening condition with high mortality, which requires enhanced clinical awareness. An early diagnosis and identification of potential triggering factors is essential. Once the diagnosis of CAPS is confirmed, aggressive treatment is mandatory in order to prevent serious thrombotic events.

4.5 MANAGEMENT OF APS

Treatment decisions in APS fall into four main areas: prophylaxis, prevention of further thromboses of large vessels, management of pregnancy in association with aPL and treatment of acute thrombotic microangiopathy, mainly CAPS.

Despite the accumulating data that aPL is a serious risk factor for thrombosis, to date no study has addressed the prophylactic management of aPL-positive individuals.There is no available data to identify which patients with aPL will suffer thromboses. Certainly, any factors predisposing the patient to thrombosis (i.e. hypertension, oral contraceptives, diabetes, smoking, hyperlipidemia) should be controlled and prophylaxis during high-risk periods (such as surgical interventions or prolonged immobilization) is crucial (116).

The different options with respect to primary thromboprophylaxis of aPL-positive subjects are: no treatment, aspirin, anti-malarials and low-intensity oral anticoagulants. Low-dose aspirin (75-100 mg) is generally used for primary thrombosis prevention; however, until the results of ongoing controlled primary prevention trials are available, physicians should be aware that the need for and the effectiveness of aspirin is not yet supported by the scientific literature (117).

The anti-platelet effects of anti-malarials (hydroxychloroquine/ chloroquine) are well established. Wallace et al. (118) showed that SLE patients and patients positive for aPL taking hydroxychloroquine had fewer thromboses than SLE and aPL-positive patients without this drug. These observations were confirmed in a more recent prospective study (119) .

A prospective study with aspirin compared with low-dose warfarin plus aspirin, is ongoing in the United Kingdom. The hypothesis to be tested is that treatment with low-dose aspirin (75 mg/day) combined with low intensity oral anticoagulation (INR=1.5) will lead to a lower rate of thrombosis than that achieved with low-dose aspirin alone in aPL positive subjects with SLE or adverse pregnancy history but without previous thrombosis (117).

Thrombosis of the placental vasculature and defective embryonic implantation represent the biological rationale for the efficacy of unfractionated or low molecular-weight heparins (LMWH) in the treatment of recurrent early abortions and fetal deaths in women with aPL. A recent systematic review of 13 randomized or quasi-randomized APS pregnancy trials involving 849 pregnant women demonstrated that the combination of aspirin (75-81 mg/d) and unfractionated heparin (5000 units subcutaneously twice daily) significantly reduced pregnancy loss compared with aspirin alone (RR, 0.46; 95% CI, 0.29-0.71) (120). Aspirin should be started with attempted conception and heparin should be started when a viable intrauterine pregnancy is documented and continued until late in the third trimester (121). Heparin administration is well tolerated and, in general, does not decrease bone density.

The effectiveness of oral anticoagulation over aspirin alone in prevention of thrombosis in (non-pregnant) SLE patients with aPL and thrombosis has been established in retrospective controlled studies (122-125). Two randomized clinical trials (126-127) have demonstrated no superiority of high intensity (target INR 3.1−4.0) over moderate-intensity warfarin (INR 2.0−3.0) for secondary prevention, and an increased risk of minor bleeding in the high-intensity arm (28% vs. 11%) (127). Their results, however, are limited in that most patients (>70%) had a history of venous – rather than arterial – thrombosis, and that patients who already had recurrent events on oral anticoagulation were excluded. Conversely, retrospective studies including more patients with previous arterial thrombosis or stroke have concluded that high-intensity warfarin is more efficacious in secondary prevention of thrombosis without increasing the risk for major bleeding (122,123, 128,129).

Based on current data, recently an International European Committee of experts proposed that in patients with APS and a first event of venous thrombosis oral anticoagulation should target INR 2.0−3.0. In the case of arterial or recurrent thrombosis, high-intensity anticoagulation (target INR 3.0−4.0) is warranted (130).

Patients with recurrent thrombotic events despite warfarin pose a challenge for clinicians. The INR at the time of recurrence is important; an INR below the target therapeutic range represents inadequate anticoagulation as opposed to warfarin or acenocumarol failure. These patients may be treated in the same manner as a patient presenting with new thrombosis without oral anticoagulation. Possible treatment options for recurrent thrombosis despite oral anticoagulation in the target INR range include increasing the intensity of anticoagulation (from 2.5-3.5 to 3.0 to 4.0), switching from oral anticoagulation to therapeutic doses of unfractionated heparin or LMWH, or adding an antiplatelet agent to oral anticoagulation (121).

Thrombocytopenia in APS rarely requires treatment. However, when this is necessary, the same treatment policy used for ITP may be considered. This treatment includes high dose corticosteroids, immunomodulating agents, and iv immunoglobulins. When steroids or immunosuppressive agents are unsuccessful, other therapeutic options have been anecdotally reported, including aspirin, rituximab (anti-CD20 monoclonal antibody) or splenectomy (131).

The optimal management of CAPS is not known but must have three clear aims: to treat any precipitating factors (prompt use of antibiotics if infection is suspected, amputation of any necrotic organ, high awareness in patients with APS who undergo an operation or an invasive procedure), to prevent and to treat ongoing thrombotic events and to suppress the excessive cytokine “storm”. Analysis of the largest series of patients with CAPS shows that the combination of anticoagulation plus steroids plus plasma exchange and/or iv immunoglobulins has the highest survival rate (70%) (110).

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5. HYPOTHESIS

APS is an acquired prothrombotic syndrome characterized by venous or arterial thromboses and pregnancy morbidity. It can present as primary APS without any discernable underlying disease, or in association with systemic autoimmune disease (usually SLE), infections (mainly chronic viral infections) and malignant process, among others. It may also occur rapidly over days or weeks, when it is known as CAPS.

Although 20 years have passed since the syndrome was recognized, several clinical aspects remain undefined. Our hypothesis is that APS is a condition with a wide spectrum of clinical presentations, including a “primary” variety that can occasionally evolve into SLE, an association with certain malignancies and a “catastrophic” variety that can appear during pregnancy and the puerperium.

6. OBJECTIVES

6.1 Objectives of the first study

Long-term follow-up in 128 patients with primary antiphospholipid syndrome

Do They Develop Lupus?. Medicine (Baltimore) 2005;84:225–230

To analyze the clinical and serologic features at the baseline and during follow-up in a large cohort of patients suffering from primary APS and to observe whether patients develop SLE or other autoimmune disease after a long-term follow-up.

6.2 Objective of the second study

Antiphospholipid antibodies associated with malignancies: Clinical and pathological characteristics of 120 patients. Semin Arthritis Rheum 2006; 35:322-32

To describe the clinical characteristics and the immunological profile of patients with malignancies having aPL, with special emphasis on the thrombotic manifestations, outcome, and treatment.

6.3. Objective of the third study

Catastrophic antiphospholipid syndrome during pregnancy and puerperium: maternal and fetal characteristics of 15 cases. Ann Rheum Dis 2007; 66:740-46

To assess the clinical and laboratory characteristics of catastrophic APS triggered or presented during pregnancy and the puerperium with special interest in maternal and fetal outcome.

7. PATIENTS AND METHODS

7.1 First study

The initial inception cohort included 201 patients from 4 different tertiary hospitals in the United Kingdom, Mexico, and Spain, who were diagnosed from 1987 onwards with primary APS (103 from Lupus Unit, St Thomas' Hospital, London, UK; 50 from Rheumatology Unit, Instituto Nacional de Cardiología, Ignacio Chávez, Mexico City, Mexico; 30 from Hospital Regional Universitario Carlos Haya, Málaga, Spain; and 18 from Hospital Reina Sofía, Córdoba, Spain).

Seventy-three patients were not included for the final analysis because they were lost to follow-up and/or because they had only 1 visit (second expert's opinion) (n = 64) or because they did not fulfill the Sapporo International Classification Criteria (n = 9).

The final study sample included 128 patients with primary APS (55 patients from London, 35 patients from Mexico, 22 from Málaga, and 16 from Córdoba). The patients attended the referral centers between January 1987 and July 2001. Clinical and serologic characteristics were reviewed according to a pre-established protocol.

To avoid including patients with secondary APS, we used the exclusion criteria for diagnosis of primary APS suggested by Piette et al (18). Patients were considered to have SLE if they fulfilled 4 or more of the ACR criteria.

Laboratory tests were performed at referral centers to which the patients were referred. Different autoantibodies (ANAs, dsDNA, ENA) were determined by conventional methods. IgG and IgM aCL were determined by ELISA and LA was determined by kaolin clotting time, dilute Russell viper venom time (DRVVT), and DRVVT confirm test using international guidelines. Levels of protein S and protein C were determined at each referral center.

7.2 Second study

One hundred and twenty patients with aPL related with malignancies were included. Seventeen cases from the CAPS Registry included until December 2003 were analyzed. The CAPS Registry, is a Web-based international registry recently created by the European Forum on Antiphospholipid Antibodies, a study group devoted to the development of multicenter projects with large populations of APS patients.

The remaining 103 cases were identified after a careful computer-assisted search of the literature (MEDLINE, National Library of Medicine, Bethesda, MD) .We included all cases of malignancies having aPL published in English, Spanish, French, German, and Italian. From 1966 to 1983, we included cases with malignancies and false-positive test for syphilis and/or LA. From 1983 (when APS was first defined), we also included cases with aCL, and from 1990 through November 2003, we also included cases with β_2GPI. Data from these articles were summarized using a standardized data form, including gender, age, diagnosis of the underlying condition, type of neoplasm, the major thrombotic clinical manifestations, immunological features, treatment, and evolution.

7.3 Third study

We reviewed the 255 cases included in the website based CAPS Registry on 1 November 2005. Patients included in the CAPS Registry fulfill the classification criteria for CAPS (19). Cases were summarized using a standardized data form, including age, diagnosis of the underlying condition, time of presentation of CAPS features (during pregnancy or the puerperium), clinical manifestations, serological features, treatment and outcome. We selected those patients who developed CAPS during pregnancy and the puerperium. The list of precipitating factors in the CAPS registry was used as a guide for case identification; however, only those cases with a close relationship between pregnancy and/or the puerperium and the development of the CAPS event were included. The diagnosis of HELLP (hemolysis, elevated

liver enzymes and low platelets) syndrome was established if patients fulfilled the laboratory criteria proposed by Sibai and colleagues (132) which include: (1) platelet count,100.000/ mm3, (2) aspartate aminotransferase >70 IU/l and (3) lactate dehydrogenase >600 U/l.

The severity of HELLP syndrome was classified according to Martin's criteria (133) based on platelet count. Class 1 (severe) was considered when platelet count was <50.000/mm3, class 2 (moderate) when platelet count was between 50.000 and 100.000/mm3 and class 3 (mild) when platelet count was >100.000/mm3.

8. ORIGINAL PAPERS

8.1 LONG-TERM FOLLOW-UP IN 128 PATIENTS WITH PRIMARY ANTIPHOSPHOLIPID SYNDROME ¿DO THEY DEVELOP LUPUS?.

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Medicine (Baltimore): 2005;84:225–230

Long-Term Follow-Up in 128 Patients With Primary Antiphospholipid Syndrome

Do They Develop Lupus?

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Abstract: We retrospectively studied a large cohort of patients with primary antiphospholipid syndrome (APS) from 4 different referral centers to analyze the clinical and serologic features and, specifically, to determine the number of patients going on to develop systemic lupus erythematosus (SLE) or other autoimmune disease after long-term follow-up.

The study included 128 unselected patients with primary APS who fulfilled the Sapporo International Criteria from 4 different tertiary hospitals in the United Kingdom, Mexico, and Spain. The patients had attended the referral centers between January 1987 and July 2001. We reviewed clinical and serologic characteristics according to a pre-established protocol. We used univariate analysis with the chi-squared or Fisher exact test and logistic regression to analyze possible factors related to the coexistence of SLE and APS.

Ninety-seven female and 31 male patients fulfilled the criteria, with a median age of 42 ± 12 years (range, 16–79 yr), and with a mean follow-up of 9 ± 3 years (range, 2–15 yr). The main manifestations included deep vein thrombosis in 62 patients (48%), arterial thrombosis in 63 (49%) patients, pregnancy loss in 177/320 (55%) cases, and pulmonary embolism in 37 (30%) patients. Other clinical manifestations were migraine in 51 (40%) patients, thrombocytopenia in 48 (38%), livedo reticularis in 47 (37%), and valvular disease in 27 (21%). Serologic findings were anticardiolipin antibodies (aCL) IgG positive in 110 (86%) patients, aCL IgM in 36 (39%), lupus anticoagulant in 71 (65%), antinuclear antibodies in 47 (37%), and positive Coombs test in 5 (4%) patients. During the follow-up and after a median disease duration of 8.2 years (range, 1–14 yr), 11 (8%) patients developed SLE, 6 (5%) developed lupus-like disease, and 1 (1%) developed myasthenia gravis. The remaining 110 patients (86%) continued to have primary APS. After the univariate analysis, a family history of lupus, the presence of Raynaud phenomenon, migraine, psychiatric features, multiple sclerosis-like features, hemolytic anemia, low C3 and C4, and Coombs positivity conferred a statistically significant risk for the subsequent development of SLE ($p < 0.05$). Only the presence of Coombs positivity had statistical significance (odds ratio, 66.4; 95% confidence interval, 1.6–2714; $p = 0.027$) after the logistic regression evaluation.

The current study confirms that progression from primary APS to SLE or lupus-like disease is unusual, even after a long follow-up. Only 3 patients developed anti-dsDNA antibodies. The presence of a positive Coombs test might be a marker for the development of SLE in patients with primary APS.

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Abbreviations: aCL = anticardiolipin antibodies, ANA = antinuclear antibodies, aPL = antiphospholipid antibodies, APS = antiphospholipid syndrome, ENA = extractable nuclear antigens, INR = International Normalized Ratio, LLD = lupus-like disease, MRI = magnetic resonance imaging, MS = multiple sclerosis, SLE = systemic lupus erythematosus, TIA = transient ischemic attack.

INTRODUCTION

In 1983, Hughes[22] described the association between thrombosis and antiphospholipid antibodies (aPL) in patients with systemic lupus erythematosus (SLE). Hughes and colleagues[20] proposed later that the combination of both venous and arterial events, often accompanied by thrombocytopenia, in the presence of aPL be termed *antiphospholipid syndrome* (APS), and where occurring in patients without features of SLE or other connective tissue disease, *primary antiphospholipid syndrome*[3]. Since the early description of primary APS, few studies have analyzed the long-term follow-up of these patients[16,36].

We retrospectively studied one of the largest known cohorts of patients with primary APS from 4 different

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referral centers, to analyze the clinical and serologic features at the beginning and during follow-up and observe if the patients develop SLE or other autoimmune disease after a long-term follow-up.

PATIENTS AND METHODS

The initial inception cohort included 201 patients from 4 different tertiary hospitals in the United Kingdom, Mexico, and Spain, who were diagnosed in 1987 as having primary APS (103 from Lupus Unit, St Thomas' Hospital, London, UK; 50 from Rheumatology Unit, Instituto Nacional de Cardiología Ignacio Chávez, Mexico City, Mexico; 30 from Hospital Regional Universitario Carlos Haya, Málaga, Spain; and 18 from Hospital Reina Sofía, Córdoba, Spain). Seventy-three patients were not included for the final analysis because they were lost to follow-up and/or because they had only 1 visit (second expert's opinion) (n = 64) or because they did not fulfill the Sapporo International Classification Criteria (n = 9) established in 1999[50]. The final study sample included 128 patients with primary APS (55 patients from London, 35 patients from Mexico, 22 from Málaga, and 16 from Córdoba). The patients attended the referral centers between January 1987 and July 2001. Clinical and serologic characteristics were reviewed according to a pre-established protocol.

To avoid including patients with secondary APS, we used the exclusion criteria for diagnosis of primary APS suggested by Piette et al[39], including clinical SLE features (malar or discoid rash, oral or pharyngeal ulceration, arthritis, pleuritis in the absence of pulmonary embolism, pericarditis, persistent proteinuria greater than 0.5 g per day related to glomerulonephritis and lymphopenia) and serologic features (antibodies to native DNA, antibodies to extractable nuclear antigens [ENA] and antinuclear antibodies [ANA] >1:320). We considered patients to have SLE if they fulfilled 4 or more of the ACR criteria[47].

The different laboratory tests were performed at the centers to which the patients were referred. ANA were determined by indirect immunofluorescence assay using mouse liver and Hep-2 cells as substrate. Anti-dsDNA antibodies were determined with the Farr ammonium sulphate precipitation technique and indirect immunofluorescence assay with *Crithidia luciliae* as substrate. ENA including anti-Ro, anti-La, anti-Sm, and anti-RNP were detected by counter-immunoelectrophoresis using calf and rabbit thymus and human spleen extracts. All centers used standardized methods to measure aPL according to APS workshop recommendations[21]. Anticardiolipin antibodies (aCL) IgG and IgM were determined by an enzyme-linked immunosorbent assay (ELISA) as described by Gharavi et al[18]. Lupus anticoagulant was determined by kaolin clotting time, dilute Russell viper venom time (DRVVT), and DRVVT confirm test using international guidelines[19]. Levels of protein S and protein C were determined at each referral center. Ninety-three of the 128 patients underwent echocardiographic examination, and 51 underwent cerebral magnetic resonance imaging (MRI) assessment.

Statistical Analysis

Data were analyzed using SPSS 11.0. Univariate analysis, using the chi-squared or Fisher exact test, and logistic regression were done to analyze possible factors related to the coexistence of SLE and APS. All tests used a 2-tailed significance level (α) of 0.05.

RESULTS

General Characteristics

Ninety-seven female and 31 male patients fulfilled APS criteria, with a median age of 42 ± 12 years (range, 16–79 yr). Patients had a mean follow-up of 9 ± 3 years (range, 2–15 yr). Only 15 patients (12%) had a family history of APS-related disorders including previous history of thrombosis in 7 (46%) family members, SLE in 4 (26%), APS in 1 (6%), and other systemic autoimmune disease in 3 (20%) family members. The main thrombotic risk factors were hypertension in 32 (25%) patients, smoking in 30 (23%), hypercholesterolemia or hyperlipidemia in 15 (12%), recent surgery or trauma in 12 (9%), oral contraceptive pill use in 9 (7%), obesity in 8 (6%), and diabetes mellitus in 2 (2%) patients. The most frequent initial APS manifestations were deep vein thrombosis (33%), pregnancy loss (23%), and stroke (13%).

Thrombotic Manifestations

Sixty-two (48%) patients had episodes of deep vein thrombosis. Nineteen patients had relapsing deep vein thrombosis with 2 or more episodes. Thirty-seven (29%) patients suffered from pulmonary embolism, accompanied in 15 (12%) cases by pulmonary hypertension. Other venous events were superficial thrombosis in 7 (5%) patients and hepatic thrombosis in 1 (1%) patient. Arterial occlusions were more frequent, being present in 63 (49%) patients, including 33 (26%) strokes and 29 (23%) transient ischemic attacks (TIAs). Other central nervous system manifestations were epilepsy in 21 (16%) patients, multiple sclerosis (MS)-like features in 10 (8%), cognitive dysfunction (mainly memory problems) in 10 (8%), diplopia in 9 (7%), psychiatric features in 7 (5%), chorea in 5 (4%), dysarthria in 4 (3%), and transverse myelitis in 1 (1%) patient. Fifty-one patients underwent cerebral MRI because of their clinical features; the images showed ischemic or infarction lesions in 28 (55%) patients, nonspecific changes in 8 (16%), and cerebral atrophy in 1 (2%) patient; images were normal in 14 (27%) patients. Coronary artery disease with myocardial infarction occurred in 8 (6%) patients, and angina pectoris in 5 (4%). Other manifestations were retinal arterial thrombosis with

amaurosis fugax in 11 (9%) patients, kidney microangiopathy in 4 (3%), ischemic bowel disease in 1 (1%), pulmonary hemorrhage in 1 (1%), and kidney thrombosis after renal transplantation in 1 (1%) patient.

By far, the most common skin manifestation was livedo reticularis, found in 47 (37%) patients, and associated in 13 cases with TIAs, stroke, or chorea. Other cutaneous manifestations were chronic ulcers in 14 (11%) patients and skin ischemic lesions in 4 (3%) patients.

Ninety-three patients had a baseline transthoracic echocardiographic evaluation, which was normal in 61 (66%) cases. Eighteen (19%) patients had mitral valve disease, 7 (8%) had aortic valve disease, and 4 (4%) patients had combined changes of mitral, aortic, and tricuspid valve involvement. Ischemic changes were found in 2 (2%) patients, and other structural abnormalities were found in 2 (2%) patients.

Obstetric History

There were a total of 320 pregnancies in our cohort of 97 women, many of them collected from St Thomas' Hospital Lupus Unit, a referral center for pregnant women with APS. Pregnancy loss occurred in 177 (55%) pregnancies, prematurity in 7 (4%) and preeclampsia in 3 (1%). During the follow-up, 9 of 97 women had 24 new successful pregnancies, while 7 patients had 10 new pregnancy loss.

Serologic Data

Evaluating other states of hypercoagulability, 4 (3%) of our patients had a deficiency of protein S and 3 (2%) patients had deficiency of protein C activity. Forty-seven (37%) patients had positive ANA in low titers (<1/160): of these patients, only 15 (11%) had titers above 1/160 after the follow-up. Only 3 (2%) patients developed anti-dsDNA antibodies; ENA antibodies were present in 3 (2%) patients during the follow-up. Complement levels including C3 and C4 were low in 4 (3%) and 20 (15%) patients, respectively. Forty-eight patients (38%) had thrombocytopenia; hemolytic anemia was present in 6 (5%), accompanied by positive Coombs tests in 5 (4%) cases. Lupus anticoagulant was present in 71 (65%) patients, aCL IgG was positive in 110 (86%), and aCL IgM was positive in 36 (39%) patients.

Treatment

Oral anticoagulation was the most frequent treatment, used in 100 (78%) patients. All pregnant women who required anticoagulation received low molecular weight heparins. Platelet antiaggregants were used in 95 (75%) patients, in 20 patients as a sole therapy; steroids were used in 10 (8%); and antimalarials in 11 (9%) patients. Other treatments used were antiepileptics in 16 (12%) patients, lipid-lowering drugs in 7 (5%), antihypertensive drugs in 6 (4%), and pulmonary thromboendarterectomy in 3 (2%) patients.

Follow-Up and Outcome

In 27 patients a new heart ultrasound evaluation was performed. New echocardiographic findings were found in 6 (22%) patients. Two patients had mitral valve disease; 2, ischemic changes; 1, aortic valve disease; and 1 patient developed mitral and aortic valve disease. Twenty-one patients had a new cerebral MRI evaluation during follow-up. MRI disclosed new abnormal findings in 8 (38%) patients, including ischemic changes in 5 (24%), nonspecific changes in 2 (10%), and small cerebral hemorrhage in 1 (5%) patient.

After a median disease duration of 8.2 years (range, 1–14 yr), 110 (86%) patients remained with primary APS; 11 (8%) patients developed SLE; 6 (5%), lupus-like disease (LLD); and 1 (1%), myasthenia gravis. Clinical and serologic details of SLE and LLD patients are shown in Table 1. To detect which clinical or serologic characteristics were related with the subsequent development of SLE, we performed a statistical analysis. After the univariate analysis, the family history of SLE, the presence of Raynaud phenomenon, migraine, psychiatric features, MS-like features, hemolytic anemia, low C3 and C4, and Coombs positivity conferred a statistically significant risk for the subsequent development of SLE ($p < 0.05$). However, after the logistic regression, only the presence of Coombs positivity showed statistical significance (odds ratio, 66.4; 95% confidence interval, 1.6–2714; $p = 0.027$) (Table 2).

Hemorrhagic complications were unusual, despite anticoagulation with target International Normalized Ratio (INR) around 3.0 in most patients: 1 patient had hemoperitoneum, 1 had epistaxis, 1 had small cerebral hemorrhage, and 1 had hemarthrosis.

At the end of the study, 113 (88%) patients were alive and 15 (12%) patients had died. The main cause of death was pulmonary embolism in 4 patients and pulmonary hemorrhage, myocardial infarction, fatal arrhythmia, and stroke in 1 case each. One patient died after a valve replacement, and 1 patient after renal transplantation. Catastrophic APS was present in only 1 case, a 38-year-old-woman from Mexico with valvular heart disease, livedo reticularis, stroke, and kidney microangiopathy who died in spite of anticoagulation treatment. In the remaining 4 cases, the causes of death were unknown.

DISCUSSION

In 1983, Hughes[22] first described patients with the combination of clinical features associated with the presence of aPL. These features included a tendency to both arterial and venous thrombosis, livedo reticularis, recurrent abortions, and, occasionally, thrombocytopenia[23]. Now, APS is a well-known clinical entity[5,28]. Although the original descriptions were mainly in patients affected by SLE, the concept of primary APS without the association with another autoimmune disease was immediately recognized[22]. A 1998

TABLE 1. Clinical and Laboratory Characteristics of Patients With Primary APS who Developed SLE or LLD

Patient	Age/Sex (yr)	Dx PAPS	New Clinical Finding	New Laboratory Feature	Dx SLE/LLD
1	43/F	1995	GMN Type V	ANA+ 80, Ro+	1999
2	30/F	1989	Discoid lupus	ANA+ 160, anemia, thrombocytopenia	1999
3	52/F	1994	Raynaud phenomenon, alopecia	ANA+ 80, dsDNA+	1998
4	35/F	1993	Malar rash, epilepsy, pleural effusion	ANA+ 80, low C4	2000
5	44/F	1986	GMN type III, pleural effusion	ANA+ 320, lymphopenia, hemolytic anemia	2000
6	58/M	1993	Photosensitivity, fatigue, myalgia	ANA+ 40, dsDNA+, thrombocytopenia	1999
7	40/F	1987	Malar rash, arthralgia, mouth ulcers, photosensitivity	ANA+ 160	1999
8	43/F	1986	Malar rash, fatigue, mouth ulcers	ANA+ 40, lymphopenia	2000
9	56/F	1986	Photosensitivity, alopecia, mouth ulcers	ANA+ 80	1998
10	37/F	1992	Alopecia	ANA+ 160, lymphopenia, Sm+, Ro+, La+	1999
11	38/F	1990	Seizures, myelopathy	ANA+ 80, dsDNA+, RNP+, lymphopenia	1998
12	45/F	1996	Seizures, arthralgia	ANA+ 160, lymphopenia	1997
13	30/M	1997		ANA+ 320	2001
14	47/F	1994	Panniculitis	ANA+ 320	2001
15	48/F	1994		ANA+ 320, thrombocytopenia	2001
16	27/M	1988		ANA+ 320, lymphopenia	2000
17	50/F	1990	Raynaud phenomenon	ANA+ 80, low complement	2001

Abbreviations: ANA = antinuclear antibodies, dsDNA = double-stranded DNA, Dx = diagnosis, GMN = glomerulonephritis, LLD = lupus-like disease, PAPS = primary antiphospholipid syndrome, SLE = systemic lupus erythematosus.

consensus workshop held in Sapporo, Japan, provided simplified criteria for the classification of APS[50]. Exclusion criteria for primary APS have been proposed by Piette et al[39] to distinguish such cases related to SLE.

Few studies have been published to date with long-term follow-up in patients with primary APS[16,41,46]. To our knowledge, the current study is the largest cohort of patients (n = 128) with a mean follow-up of 9 years.

We found a wide variety of thrombotic manifestations; however, some specific aspects deserve to be discussed in detail. We found a high prevalence of neurologic events in our patients: 40% had migraine, 26% developed stroke, 23%

TABLE 2. Univariate and Multivariate Analysis of Potential Clinical and Serologic Markers for the Development of SLE in Patients With Primary APS

	Univariate Analysis			Multivariate Analysis (Logistic Regression)		
	OR	95% CI	p Value	OR	95% CI	p Value
Family history of SLE	12.7	2–82.2	0.002	4.7	0.07–293	0.45
Raynaud phenomenon	4.5	1.2–16.8	0.01	2.5	0.2–23	0.39
Migraine	4.5	1.2–16.7	0.01	2.5	0.2–24.7	0.42
Psychiatric features	4.9	0–26.2	0.05	4.6	0.3–61.4	0.24
MS-like features	5.5	1.3–24.1	0.01	0.1	0.001–21	0.49
Hemolytic anemia	14.2	2.8–73.5	0.0002	0.7	0.01–52.3	0.91
Coombs positive	59.2	7.0–Infinite	0.0001	66.4	1.6–2714	**0.027**
Low C3	9.7	1.5–63	0.01	4.5	0.07–288	0.47
Low C4	6.8	1.8–25	0.002	0.7	0.05–10.2	0.83

Abbreviations: See Table 1. OR = odds ratio; CI = confidence interval; MS = multiple sclerosis.

presented TIAs, and 16% had seizures. A 2003 study showed a significant association between the presence of aPL and cerebrovascular accidents, migraine, and seizures[42]. A high proportion of patients (33 of 53) who underwent cerebral MRI had small high-intensity lesions suggestive of vasculopathy, but only 10 (8%) patients developed some degree of cognitive impairment. Recently, Vermeer et at[48,49], in a selected non-aPL elderly population, demonstrated a close relationship between the presence of small silent infarcts and the subsequent appearance of dementia, cognitive function decline, and stroke. An noteworthy observation is the presence of MS-like features in 10 of our patients with primary APS. Cuadrado et al[13] described 27 patients with APS with neurologic symptoms that mimicked MS.

Recurrent pregnancy loss is a common health problem affecting 1%–2% of women of reproductive age; APS is the main treatable cause of recurrent miscarriages. The relation between aPL and recurrent pregnancy loss is well established[15,24,27,29,32,33,38] and is commonly associated with the presence of placental infarction and thrombotic changes in decidual microvessels. Pregnancy losses in patients with APS frequently occur after 10 weeks, compared with spontaneous abortions not associated with aPL, which most often occur earlier[31]. The past medical history of successful deliveries was lower in our cohort (45%) compared with that in other series[9,10]; a possible reason for the difference is that our principal study center is a referral center for women with a history of 3 or more miscarriages or 1 or more fetal deaths in association with aPL. Primary APS has also been associated in other series with prematurity[38] and with the development of preeclampsia[8]. A previous history of these 2 last complications was not noted in our patients.

In patients with APS, serious bleeding complications may occur, but the risk, despite elevated levels of INR, is not higher than that found in other thrombotic conditions warranting oral anticoagulation. We had only 4 patients with severe bleeding (hemoperitoneum, hemarthrosis, small cerebral hemorrhage, and epistaxis). Concomitant drugs, mainly aspirin, and high blood pressure could increase the risk of bleeding in APS patients[11], but previous studies have shown that the risk of recurrent thrombosis with INR <3.0 is higher than the risk of bleeding[26]. The mortality rate in the current study was slightly higher (12%) than in similar studies (8%–10%) with long-term follow-up of patients with aPL[37,44]. We had only 1 patient with the life-threatening condition known as catastrophic APS.

Several studies have suggested that some patients with primary APS may go on to develop characteristics of SLE. To date, there are about 30 cases reported of patients whose primary APS evolved into SLE or LLD[1,2,4,7,10,14,17,34,35,40,43,45]. Mujic et al[35] followed a group of 80 patients with primary APS during a median period of 78 months; from these, 1 patient developed LLD after 4 years and 2 cases evolved into SLE more than 10 years after the initial presentation of primary APS. Carbone et al[10] described 3 cases of 33 patients with primary APS who developed features of LLD or SLE after 6 years of follow-up. Gattorno et al[17] studied a childhood cohort of 14 patients with primary APS with a mean follow-up of 6 years, and described 2 patients (1 boy and 1 girl) who developed SLE and 1 patient who developed LLD.

We describe here 16 cases (11 with SLE and 5 with LLD) who developed clinical and/or serologic features of a ''new'' autoimmune disease after long-term follow-up and 1 patient who developed features of myasthenia gravis. After statistical analysis we found that the presence of a positive Coombs test was a marker for the development of SLE in patients with primary APS. Cervera et al[12], in a European cohort of 1000 patients with APS, reported that patients with APS associated with SLE had a higher prevalence of arthritis, livedo reticularis, thrombocytopenia, and leukopenia than patients with primary APS. However, we did not find these features as markers for the development of SLE in our primary APS patients.

In conclusion, we believe that progression from primary APS to SLE or LLD is unusual. Perhaps the transitional period is long. Therefore, regular follow-up is warranted in patients with APS. It is important to emphasize some limitations of our study: first, our principal study center is a referral center for pregnant women with APS; second, the mortality rate was relatively high because all patients who died came from a cardiovascular center participating in the study; and, finally, the study was retrospective.

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REFERENCES

1. Alarcon-Segovia D, Perez-Vasquez ME, Villa AR, Drenkard C, Cabiedes J. Preliminary classification criteria for the antiphospholipid syndrome within systemic lupus erythematosus. *Semin Arthritis Rheum*. 1992;21:275–286.
2. Andrews PA, Frampton G, Cameron JS. Antiphospholipid syndrome and systemic lupus erythematosus. *Lancet*. 1993;342:988–989.
3. Asherson RA. A ''primary'' antiphospholipid syndrome? *J Rheumatol*. 1988;15:1741–1746.
4. Asherson RA, Baguley E, Pal C, Hughes GRV. Antiphospholipid syndrome: five year follow up. *Ann Rheum Dis*. 1991;50:805–810.
5. Asherson RA, Cervera R, Piette JC, Shoenfeld Y. The Antiphospholipid Syndrome. Boca Raton, FL: CRC Press; 1996.
6. Asherson RA, Khamashta MA, Ordi-Ros J, Derksen RH, Machin SJ, Barquinero J, Outt HH, Harris EN, Vilardell-Torres M, Hughes GR. The ''primary'' antiphospholipid syndrome: major clinical and serological features. *Medicine (Baltimore)*. 1989;68:366–374.
7. Blanco Y, Ramos-Casals M, Garcia-Carrasco M, Cervera R, Font J, Ingelmo M. Sindrome antifosfolipidico primario que evoluciona a lupus eritematoso sistemico: presentacion de tres nuevos casos y revision de la literatura. *Rev Clin Esp*. 1999;199:586–588.
8. Branch DW, Andres R, Digre KB, Rote NS, Scott JR. The association of

antiphospholipid antibodies with severe preeclampsia. *Obstet Gynecol*. 1989;73:541–545.
9. Branch DW, Silver RM, Blackwell JL, Reading JC, Scott JR. Outcome of treated pregnancies in women with antiphospholipid syndrome: an update of the Utah experience. *Obstet Gynecol*. 1992;80:614–620.
10. Carbone J, Orera M, Rodriguez-Mahou M, Rodriguez-Perez C, Sanchez-Ramon S, Seoane E, Rodriguez JJ, Zabay JM, Fernandez-Cruz E. Immunological abnormalities in primary APS evolving into SLE: 6 years follow-up in women with repeated pregnancy loss. *Lupus*. 1999;8: 274–278.
11. Castellino G, Cuadrado MJ, Godfrey T, Khamashta MA, Hughes GRV. Characteristics of patients with antiphospholipid syndrome with major bleeding after oral anticoagulant treatment. *Ann Rheum Dis*. 2001;60: 527–530.
12. Cervera R, Piette JC, Font J, Khamashta MA, Shoenfeld Y, Camps MT, Jacobsen S, Lakos G, Tincani A, Kontopoulou-Griva I, Galeazzi M, Meroni PL, Derksen RH, de Groot PG, Gromnica-Ihle E, Baleva M, Mosca M, Bombardieri S, Houssiau F, Gris JC, Quere I, Hachulla E, Vasconcelos C, Roch B, Fernandez-Nebro A, Boffa MC, Hughes GR, Ingelmo M; Euro-Phospholipid Project Group. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. *Arthritis Rheum*. 2002;46: 1019–1027.
13. Cuadrado MJ, Khamashta MA, Ballesteros A, Godfrey T, Simon MJ, Hughes GRV. Can neurologic manifestations of Hughes (antiphospholipid) syndrome be distinguished from multiple sclerosis? Analysis of 27 patients and review of the literature. *Medicine (Baltimore)*. 2000;79: 57–68.
14. Derksen RHWM, Gmelig-Meijling FHJ, de Groot PG. Primary antiphospholipid syndrome evolving into systemic lupus erythematosus. *Lupus*. 1996;5:77–80.
15. Derksen RH, Khamashta MA, Branch DW. Management of obstetric antiphospholipid syndrome. *Arthritis Rheum*. 2004;50:1028–1039.
16. Erkan D, Yazici Y, Sobel R, Lockshin MD. Primary antiphospholipid syndrome: functional outcome after 10 years. *J Rheumatol*. 2000;27: 2817–2821.
17. Gattorno M, Falcini F, Ravelli A, Zulian F, Buoncompagni A, Martini G, Resti M, Picco P, Martini A. Outcome of primary antiphospholipid syndrome in childhood. *Lupus*. 2003;12:449–453.
18. Gharavi AE, Harris EN, Asherson RA, Hughes GRV. Anticardiolipin antibodies: isotype distribution and phospholipid specificity. *Ann Rheum Dis*. 1987;46;1–6.
19. Greaves M, Cohen H, MacHin SJ, Mackie I. Guidelines on the investigation and management of the antiphospholipid syndrome. *Br J Haematol*. 2000;109:704–715.
20. Harris EN, Baguley E, Asherson RA, Hughes GRV. Clinical and serological features of the ''antiphospholipid syndrome'' (APS) [abstract]. *Br J Rheumatol*. 1987;26:19.
21. Harris EN, Gharavi AE, Patel SP, Hughes GRV. Evaluation of the anticardiolipin antibody test: report of an international report held 4 April, 1986. *Clin Exp Immunol*. 1987;69:215–222.
22. Hughes GRV. Thrombosis, abortion, cerebral disease, and the lupus anticoagulant. *Br J Med (Clin Res Ed)*. 1983;287:1088–1089.
23. Hughes GRV, Khamashta MA. The antiphospholipid syndrome. *J R Coll Physicians Lond*. 2000;28:301–304.
24. Julkunen H, Jouhikainen T, Kaaja R, Leirisalo-Repo M, Stephansson E, Palosuo T, Teramo K, Friman C. Fetal outcome in lupus pregnancy: a retrospective case-control study of 242 pregnancies in 112 patients. *Lupus*. 1993;3:125–131.
25. Khamashta MA, ed. Hughes syndrome. Antiphospholipid syndrome. London: Springer; 2000.
26. Khamashta MA, Cuadrado MJ, Mujic F, Taub NA, Hunt BJ, Hughes GR. The management of thrombosis in the antiphospholipid antibody syndrome. *N Engl J Med.* 1995;332:993–997.
27. Khamashta MA, McKworth-Young C. Antiphospholipid (Hughes') syndrome: a treatable cause of recurrent pregnancy loss. *Br Med J*. 1997;314:244.
28. Levine JS, Branch W, Rauch J. The antiphospholipid syndrome. *N Engl J Med*. 2002;346:752–763.
29. Lima F, Buchanan NM, Khamashta MA, Kerslake S, Hughes GRV. Obstetric outcome in systemic lupus erythematosus. *Semin Arthritis Rheum*. 1995;25:184–192.
30. Lima F, Khamashta MA, Buchananan NM, Kerslake S, Hunt BJ, Hughes GR. A study of sixty pregnancies in patients with the antiphospholipid syndrome. *Clin Exp Rheumatol*. 1996;14:131–136.
31. Lockshin MD. Pregnancy loss in the antiphospholipid syndrome. *Thromb Haemost*. 1999;82:641–648.
32. Lockshin MD, Drunzin MI, Goei S, Qamar T, Magid MS, Jovanovic L, Ferenc M. Antibody to cardiolipin as a predictor of fetal distress of death in pregnant patients with systemic lupus erythematosus. *N Engl J Med*. 1985;313:152–156.
33. Lockshin MD, Qamar T, Drunzin MI, Goei S. Antibody to cardiolipin, lupus anticoagulant and fetal death. *J Rheumatol*. 1987;14:259–262.
34. Loughran T, Parke AL. Progression of primary phospholipid antibody syndrome into SLE. *J Rheumatol*. 2001;28:54(A58).
35. Mujic F, Cuadrado MJ, Lloyd M, Khamashta MA, Page G, Hughes GRV. Primary antiphospholipid syndrome evolving into systemic lupus eryhtematosus. *J Rheumatol*. 1995;22:1589–1592.
36. Munoz-Rodriguez FJ, Font J, Cervera R, Reverter JC, Tassies D, Espinosa G, Lopez-Soto A, Carmona F, Balasch J, Ordinas A, Ingelmo M. Clinical study and follow-up of 100 patients with the antiphospholipid syndrome. *Semin Arthritis Rheum*. 1999;29:182–190.
37. Ordi-Ros J, Paredes F, Mauri M. Long term follow-up in patients with lupus anticoagulant. *J Autoimmun*. 2000;15:A13.
38. Out HJ, Bruinse HW, Christiaens GCML, Van Vliet M, De Groot PG, Nieuwenhuis HK, Derksen RH. A prospective, controlled multicenter study on the obstetric risks of pregnant women with antiphospholipid antibodies. *Am J Obstet Gynecol*. 1992;167:26–32.
39. Piette JC, Wechsler B, Frances C, Papo T, Godeau P. Exclusion criteria for primary antiphospholipid syndrome [letter]. *J Rheumatol*. 1993;20: 1802–1804.
40. Queiro R, Weruaga A, Riestra JL. C4 deficiency state in antiphospholipid antibody-related recurrent preeclampsia evolving into systemic lupus erythematosus. *Rheumatol Int*. 2002;22:126–128.
41. Reshetnyak TM, Alekberova ZS, Kalashnikova LA, Alexandrova EN, Mach ES, Radenska-Lopovok SG, Kalashnikova LA, Nasonova VA. Survival and prognostic factors of death risk in antiphospholipid syndrome: 8 year follow-up. *Ter Arkh*. 2003;75:46–51.
42. Sanna G, Bertolaccini ML, Cuadrado MJ, Laing H, Khamashta MA, Mathieu A, Hughes GR. Neuropsychiatric manifestations in systemic lupus erythematosus: prevalence and association with aPL. *J Rheumatol*. 2003;30:985–992.
43. Seisedos L, Munoz-Rodriguez FJ, Cervera R, Font J, Ingelmo M. Primary antiphospholipid syndrome evolving into systemic lupus erythematosus. *Lupus*. 1997;6:285–286.
44. Shah NM, Khamashta MA, Atsumi T, Hughes GRV. Outcome of patients with anticardiolipin antibodies: A 10 year follow up of 52 patients. *Lupus*. 1998;7:3–6.
45. Silver RM, Draper ML, Scott JR, Lyon JL, Reading J, Branch DW. Clinical consequences of antiphospholipid antibodies: an historic cohort study. *Obstet Gynecol*. 1994;83:372–377.
46. Taglietti M, Biasini Rebaioli CH, Frassi M. Long term outcome in 91 patients with primary antiphospholipid syndrome (PAPS). *J Autoimmun*. 2000;15:A93.
47. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, Schaller JG, Talal N, Winchester RJ. The 1982 revised criteria for classification of systemic lupus erythematosus. *Arthritis Rheum*. 1982; 25:1271–1277.
48. Vermeer SE, Hollander M, van Dijk EJ Hofman A, Koudstaal PJ, Breteler MM; Rotterdam Scan Study. Silent brain infarcts and white matter lesions increase stroke risk in the general population. *Stroke*. 2003;34:1126–1129.
49. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. *N Engl J Med*. 2003;348:1215–1222.
50. Wilson WA, Gharavi AE, Koike T, Lockshin MD, Branch DW, Piette JC, Brey R, Derksen R, Harris EN, Hughes GR, Triplett DA, Khamashta MA. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. *Arthritis Rheum*. 1999;42:1309–1311.

8.1 Summary of results

This study described one of the largest known cohorts of patients with primary APS from 4 different referral centers. The final study sample included 128 patients with primary APS (97 female and 31 male patients).

- Median age was 42 years (range, 16-79 yr)
- Mean follow-up was 9 years (range, 2–15 yr).
- The most frequent initial APS manifestations were DVT (33%), pregnancy loss (23%), and stroke (13%).
- During follow-up, 62 (48%) patients had episodes of DVT and 19 patients had relapsing DVT with 2 or more episodes.
- Arterial occlusions were more frequent, being present in 63 (49%) patients, including 33 (26%) strokes and 29 (23%) TIA.
- Fifty-one patients underwent cerebral MRI. Abnormal findings were found in around 70% of patients (mainly ischemic lesions).
- A baseline transthoracic ecocardiography (TTE) was performed in 93 patients. The main abnormal findings were mitral and aortic valve disease in 18 (19%) and 7 (8%) patients respectively.
- Of the 320 pregnancies in our cohort of 97 women, pregnancy loss occurred in 177 (55%), prematurity in 7 (4%) and preeclampsia in 3 (1%). During the follow-up, 9 of 97 women had 24 new successful pregnancies, while 7 patients had 10 new pregnancy losses.
- Serologic findings were IgG aCL positive in 110 (86%) patients, IgM aCL in 36 (39%), LA in 71 (65%), ANAs in 47 (37%), and positive Coombs test in 5 (4%) patients. Only 3 patients developed anti-dsDNA.
- Twenty-one patients had a new cerebral MRI disclosing new abnormal findings in 8 (38%) patients

- Twenty-seven patients had a new heart ultrasound evaluation, disclosing new echocardiographic findings in 6 (22%) patients.
- After a median disease duration of 8.2 years (range, 1–14 yr), 110 (86%) patients remained with primary APS; 11 (8%) patients developed SLE; 6 (5%), LLD; and 1 (1%), myasthenia gravis.
- Logistic regression analysis showed that Coombs positivity conferred a statistically significant risk for the subsequent development of SLE (OR, 66.4; 95% CI, 1.6–2714; $p = 0.027$).
- At the end of the study, 113 (88%) patients were alive and 15 (12%) patients had died.

8.2 ANTIPHOSPHOLIPID ANTIBODIES ASSOCIATED WITH MALIGNANCIES: CLINICAL AND PATHOLOGICAL CHARACTERISTICS OF 120 PATIENTS.

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Antiphospholipid Antibodies Associated with Malignancies: Clinical and Pathological Characteristics of 120 Patients

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OBJECTIVE: To describe the different types of malignancies associated with antiphospholipid antibodies (aPL).

METHODS: We performed a computer-assisted (MEDLINE, National Library of Medicine, Bethesda, MD) search of the literature from 1966 to 2003 to identify all cases of malignancies having aPL.

RESULTS: One hundred twenty patients were found. The mean age was 56 ± 17 years (range 5 to 88). Sixty-two (52%) patients were men and 58 (48%) were women. A heterogeneous group of malignancies were found. Regarding hematological malignancies, 10 (8%) patients suffered from B-cell lymphoma, 8 (7%) from spleen lymphoma, 7 (6%) from chronic myeloid leukemia, and 6 (5%) from non-Hodgkin's lymphoma (NHL). Regarding solid tumors, renal cell carcinoma was diagnosed in 7 (6%) patients, primary tumor with unknown origin in 7 (6%), lung adenocarcinoma in 6 (5%), breast carcinoma in 6 (5%), and melanoma in 6 (5%). The main aPL-related manifestations were thrombocytopenia (25%), cerebrovascular accidents (24%), deep vein thrombosis (19%), pulmonary embolism (15%), and heart valve lesions (9%). In 17 cases, catastrophic antiphospholipid syndrome was considered to be triggered by the malignancy. Seventy-one (63%) of 113 patients recovered or are still alive after cancer treatment. Twenty-three (35%) of 65 patients achieved aPL remission after proper treatment of the malignancy.

CONCLUSIONS: It is important to bear in mind, especially in elderly patients, that thrombotic events associated with aPL can be the first manifestation of malignancy. At the same time, the presence of aPL in patients with malignancies has important implications in their treatment and prognosis.

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KEYWORDS antiphospholipid syndrome, neoplasm, cancer, malignancy, antiphospholipid antibodies, anticardiolipin antibodies, lupus anticoagulant

Since the early description by Armand Trousseau in 1865 (1), the presence of a tumor has been associated with a prothrombotic state. Despite our better knowledge of the pathogenic mechanisms and the current therapeutic options, venous and arterial thromboses are still among the most common clinical complications in patients with malignancies (2).

The antiphospholipid syndrome (APS) is an acquired autoimmune prothrombotic condition, characterized by arterial and/or venous thromboses and pregnancy morbidity in the presence of antiphospholipid antibodies (aPL) (3). While, initially, APS was described in patients suffering from systemic lupus erythematosus (SLE), currently, this condition is associated with a wide variety of diseases, including other systemic autoimmune conditions (rheumatoid arthri-

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tis, systemic sclerosis, Sjögren's syndrome, systemic vasculitis), infections (human immunodeficiency virus, hepatitis C virus, Epstein–Barr virus) (4), and malignancies (solid tumors and hematological neoplasms) (5).

Several mechanisms have been suggested for the association between aPL and cancer and include the following: (1) production of autoantibodies by the immune system as a response against tumor antigens; (2) production of monoclonal immunoglobulins with lupus anticoagulant (LA) and anticardiolipin antibody (aCL) activities; and (3) secretion of aCL from tumor cells (6).

Some studies have focused on the association between aPL and solid and hematological malignancies (7-11) but with limited information of their clinical (thrombotic) presentation. The aim of the present study was to describe the clinical characteristics and the immunological profile of patients with malignancies having aPL, with special emphasis on their thrombotic manifestations, outcome, and treatment.

Patients and Methods

Patients were identified by a computer-assisted (MEDLINE, National Library of Medicine, Bethesda, MD) search of the literature to locate all cases of malignancies having aPL published in English, Spanish, French, German, and Italian. From 1966 to 1983, we included cases with malignancies and false-positive test for syphilis (BFP-STS) and/or LA. Since 1983 (when APS was first defined), we also included cases with aCL, and since 1990 through November 2003, we also included those cases with anti-beta 2-glycoprotein I antibodies (β2-GPI) (keywords: false-positive test for syphilis (BFP-STS), anticardiolipin antibodies, lupus inhibitor, coagulation inhibitor, lupus anticoagulant, beta-2-glycoprotein I antibodies, antiphospholipid syndrome, malignancy, neoplasm, tumor, and cancer).

Data from these articles were summarized using a standardized data form, including gender, age, diagnosis of the underlying condition, type of neoplasm, the major thrombotic clinical manifestations, immunological features, treatment, and evolution. The bilateral Fisher's exact test was used for statistical analysis of the outcome variables using the SPSS 10.0 program.

Results

General Characteristics

One hundred twenty patients were identified in the literature (12-96). The different types of malignancies associated with aPL are listed in Tables 1 and 2. Additionally, thrombotic manifestations, serological features, treatment, and outcome variables are described in detail in chronological order in Table 3. The mean age was 56 ± 17 years (range, 5 to 88). Sixty-two (52%) patients were men and 58 (48%) were women. Primary APS was diagnosed in 22 (18%) patients, SLE in 4 (3%), lupus-like disease in 7 (6%), autoimmune hemolytic anemia in 4 (3%), and systemic sclerosis in 2 (2%) patients. Other autoimmune conditions were found in 1 case each (ulcerative colitis, Sneddon's syndrome, sarcoidosis, Evans' syndrome, cryoglobulinemia, and idiopathic thrombocytopenic purpura). Seventeen patients presented with the catastrophic APS.

Table 1 Hematological Malignancies Associated with aPL

Type	No. (%)	References
B-cell lymphoma	10 (8)	22, 43, 53, 60, 74, 77, 78, 80
Spleen lymphoma	8 (7)	28, 36, 48, 73
Chronic myeloid leukemia	7 (6)	27, 44, 47, 65, 68, 70, 82
Non-Hodgkin's lymphoma	6 (5)	8, 46, 55, 81, 93
Lymphocytic lymphoma	4 (3)	16, 23, 24, 29
Hairy-cell leukemia	4 (3)	17, 20, 31, 49
Cutaneous T-cell lymphoma	3 (3)	21, 35, 40
Multiple myeloma	3 (3)	23, 57, 83
Hodgkin's disease	3 (3)	13, 77, 95
Acute myeloid leukemia	2 (2)	26, 96
Chronic lymphoid leukemia	2 (2)	33, 66
Lymphosarcoma	2 (2)	12, 13
Peripheral T-cell lymphoma	1 (1)	45
Waldenström macroglobulinemia	1 (1)	14
Acute lymphoid leukemia	1 (1)	30
Monoclonal gammopathy	1 (1)	23
Myeloproliferative syndrome	1 (1)	79
Acute monocytic leukemia	1 (1)	38
Angiocentric lymphoma	1 (1)	51
Lymphoplasmacytoid lymphoma	1 (1)	89

Malignancies

A heterogeneous group of malignancies was found. Regarding the hematological malignancies, 10 (8%) patients suffered from B-cell lymphoma, 8 (7%) from splenic lymphoma, 7 (6%) from chronic myeloid leukemia, 6 (5%) from non-Hodgkin's lymphoma (NHL), 5 (4%) from lymphocytic lymphoma, and 5 (4%) from hairy cell leukemia (Table 1).

Regarding solid tumors, 7 (6%) patients had renal cell carcinoma, 7 (6%) primary tumor with unknown origin, 6 (5%) lung adenocarcinoma, 6 (5%) breast carcinoma, 6 (5%) melanoma, 4 prostatic adenocarcinoma (3%), 3 (3%) otorhinolaryngology tumors, 3 (2%) non-small-cell lung cancer, 2 (2%) central nervous system tumors, 2 (2%) ovarian carcinoma, 2 (2%) colon carcinoma, and 2 (2%) cholangiocarcinoma (Table 2).

In 41 cases, the diagnosis of both conditions (APS and cancer) was made simultaneously; in 29 cases, the malignancies were diagnosed after the thrombotic manifestations of APS, and in 25 cases, APS features appeared some time after the diagnosis of cancer. In 25 cases, this particular information was not available.

Thrombotic Manifestations

A large number of thrombotic manifestations were collected, mainly large vessels thrombosis (Table 3). Clinical manifes-

Table 2 Solid Organ Malignancies Associated with aPL

Type	No. (%)	References
Renal cell carcinoma	7 (6)	15, 32, 34, 50, 77, 88, 92
Primary tumor with unknown origin	6 (5)	8, 59, 75, 84, 91
Lung adenocarcinoma	6 (5)	18, 41, 61, 69, 71, 72
Breast carcinoma	6 (5)	8, 75, 77, 90
Melanoma	6 (5)	39, 42
Prostatic adenocarcinoma	4 (3)	8, 25
Otorhinolaryngology tumors	3 (3)	8, 75
Non-small-cell lung cancer	3 (3)	8, 58, 85
Central nervous system tumors	2 (2)	63, 94
Uterine carcinoma	2 (2)	64, 68
Colon carcinoma	2 (2)	8, 90
Ovarian carcinoma	2 (2)	8, 41
Cholangiocarcinoma	2 (2)	62, 86
Leiomyoblastoma	1 (1)	33
Thymoma	1 (1)	19
Hepatocarcinoma	1 (1)	8
Mesothelioma	1 (1)	52
Tracheal carcinoma	1 (1)	54
Gastric carcinoma	1 (1)	56
Carcinoid tumor	1 (1)	76
Papillary thyroid carcinoma	1 (1)	77
Leiomyosarcoma	1 (1)	87

tations were available in 106 cases. Seventy-six (71%) patients had thrombotic manifestations; 23 (21%) fulfilled the international preliminary classification criteria for APS (Sapporo criteria) (97), while 53 patients had thrombotic manifestations with only 1 aPL (LA and/or aCL) determination. Twenty-five (24%) patients had cerebrovascular accidents (CVA), 20 (19%) deep vein thrombosis (DVT), 16 (15%) pulmonary embolism (PE), 10 (9%) valve lesions, 8 (7%) myocardial infarction, 6 (6%) spontaneous abortions, 3 (3%) peripheral artery thrombosis, 3 (3%) pulmonary infarction, 2 (2%) transient ischemic attacks, 1 (1%) superficial vein thrombosis, and 1 (1%) patient pulmonary hemorrhage. Intraabdominal manifestations were also common: 13 (12%) patients had renal involvement (in 4 cases manifested as renal thrombotic microangiopathy), 8 (7%) splenic thrombosis, 5 (5%) hepatic thrombosis, 4 (4%) mesenteric thrombosis, 4 (4%) inferior vena cava thrombosis, 4 (4%) adrenal involvement, 2 (2%) pancreatic thrombosis, 2 (2%) intestinal thrombosis, and 1 (1%) portal vein thrombosis.

Skin involvement was present in several patients: *Livedo reticularis* in 8 (7%) patients, digital necrosis or foot gangrene in 6 (6%), skin ulcers in 5 (5%), skin microthrombosis in 3 (3%), and splinter hemorrhages in 1 (1%). Other manifestations included retinal artery thrombosis (2 patients), chorea (1 patient), bone marrow necrosis (1 patient), retinal vein thrombosis (1 patient), and bone infarct (1 patient).

Laboratory Features

Thrombocytopenia was present in 27 (25%) patients, LA in 70/104 (67%), aCL in 70/104 (67%) (54 aCL IgG and 20 aCL IgM), β2-GPI in 6 (6%), BFP-STS in 5 (5%), and hemolytic anemia in 4 (4%) patients.

Treatment

Information about treatment was available in 99 cases. Most patients received more than 1 treatment. APS thrombotic manifestations were treated with anticoagulation in 38 (38%) patients, steroids in 36 (36%), cyclophosphamide in 11 (11%), plasma exchange in 9 (9%), aspirin in 6 (6%), thrombolysis in 3 (3%), dialysis in 3 (3%), intravenous immunoglobulins in 2 (2%), and azathioprine in 2 (2%) patients. Cyclosporine, vena cava filter, intravenous prostaglandins, and chloroquine were used in 1 case each. Regarding the treatment of cancer, chemotherapy was used in 33 (33%) patients and surgery in 24 (24%) including splenectomy in 12 (12%), nephrectomy in 5 (5%), lung lobectomy in 1 (1%), thyroidectomy in 1 (1%), duodenal-pancreatectomy in 1 (1%), and leg amputation in 1 (1%) patient. Other treatments used were irradiation (9%), interferon (8%), and bone marrow transplantation (2%). Fresh frozen plasma, rituximab, and danazol were used in 1 case each.

Outcome and aPL Remission

Seventy-one (63%) of 113 patients recovered or are still alive after cancer treatment. Although mortality is directly related to the neoplasm by itself, we found several thrombotic features that were related with a worst prognosis, including pulmonary infarct (0 versus 3; $P = 0.013$, chi^2), kidney involvement (5 versus 8; $P = 0.021$, chi^2), adrenal involvement (0 versus 3, $P = 0.013$; chi^2), intestinal thrombosis (0 versus 2; $P = 0.043$, chi^2), and splenic thrombosis (2 versus 6, $P = 0.009$; chi^2). Although information regarding disappearance of aPL after cancer therapy was not available in all cases, 23 (35%) of 65 patients achieved aPL remission after treatment, especially those patients with lymphoma of the spleen (5 versus 1; $P = 0.01$; chi^2) and those who underwent nephrectomy (4 versus 0; $P = 0.006$; chi^2). Interestingly, 1 patient (73) achieved remission of aPL after B cell depletion with rituximab.

Discussion

Patients with cancer represent 20% of all patients in whom DVT and PE are diagnosed (98). In cancer, tumor cells can activate the coagulation system directly, through interactions with platelets, clotting, and fibrinolytic systems to generate thrombin. A series of endothelial factors, such as fibrin and tissue factor (TF), play a role in the clotting formation mediated via fibrin deposition and platelet activation. It has been postulated that aberrant TF expression plus disregulation of mechanisms controlling TF procoagulant activity contribute to the systemic hypercoagulability inherent to many patients with cancer (99). Furthermore, other factors participate in this coagulopathic disorder, including vascular endothelial

Table 3 Clinical and Serological Characteristics of 120 Patients with Malignancies and aPL

Case (Ref.)	Neoplasm	Features Suggestive of APS	aPL†	Related Autoinmune Disease	Treatment	Outcome	Remission of the aPL*
1. (12)	Lymphosarcoma	Thrombocytop	VDRL false +		Ch	Recovery	NR
2. (13)	Lymphoblastic lymphosarcoma		VDRL false +	AHA	Splenectomy	Death	No
3. (14)	Waldenström macroglobulinemia	Multiple MI	VDRL false +		Splenectomy	Death	No
4. (15)	Renal cell carcinoma	Thrombocytop	VDRL false +	Lupus-like	S, nephrectomy	Recovery	Yes
5. (16)	Lymphocytic lymphoma		LA		Ch	Recovery	Yes
6. (17)	Hairy-cell leukemia		LA	AHA		Recovery	No
7. (18)	Lung adenocarcinoma	SH, thrombocytop	LA, aCL IgG (40), IgM (40) VDRL false +	ITP	S, plasmapheresis	Recovery	Yes
8. (19)	Thymoma	CVA, SA	aCL IgG (7.3)		AC, S, surgery	Recovery	Yes
9. (20)	Hairy cell leukemia		LA, aCL		Splenectomy	Recovery	Yes
10. (21)	Cutaneous T-cell lymphoma	Thrombocytop	LA, aCL IgG aCL IgM		S	Recovery	No
11. (22)	B-cell lymphoma	Thrombocytop	LA			Death	No
12. (23)	Multiple myeloma		LA		P, Ch	Death	No
13. (23)	Monoclonal gammopathy		LA			Recovery	NR
14. (23)	Lymphocytic lymphoma	Thrombocytop	LA		Ch	Recovery	NR
15. (24)	Lymphocytic lymphoma	SA(3), thrombocytop	LA, aCL IgG (2.3)	PAPS	S, ASA	Recovery	NR
16. (25)	Prostatic carcinoma	TMA	aCL IgG (17 GPL)	SSc	FFP, HD	Recovery	NR
17. (26)	Acute myeloblastic leukemia (M2)	Hepatic	LA		BMT, Cyclo, Irr	Death	No
18. (27)	Chronic myelomonocytic leukemia	DVT, LR, thrombocytop	aCL IgM	SLE	S, Chloroquine	Death	NR
19. (28)	Spleen lymphoplasmacytic lymphoma		LA		Ch	Recovery	NR
20. (28)	Spleen lymphoplasmacytic lymphoma		LA		Ch	Recovery	Yes
21. (28)	Spleen lymphoplasmacytic lymphoma	PE	LA, aCL IgG (5 GPL) IgM (100 MPL)		AC, splenectomy	Recovery	No
22. (28)	Spleen lymphoplasmacytic lymphoma		LA, aCL IgG (15 GPL) IgM (1000 MPL)		Ch	Recovery	NR
23. (29)	Lymphocytic lymphoma	SA, diplopia, LR Thrombocytop	aCL IgM (>60 U)	SLE	S, Ch	Recovery	Yes
24. (30)	Acute lymphoblastic leukemia	Chorea	LA		S, Ch	Recovery	Yes
25. (31)	Hairy cell leukemia	Thrombocytop	LA		Interferon-α	Death	No
26. (32)	Renal cell carcinoma	CVA	aCL		AC, nephrectomy	Recovery	Yes
27. (33)	Chronic lymphoid leukemia	LR, thrombocytop	aCL	Lupus-like	S, Cyclo	Recovery	Yes
	Leiomyoblastoma	Skin necrosis	IgG (25 IU)	AHA			
28. (34)	Renal cell carcinoma	PE	LA, aCL IgM (3.6 U)	PAPS	AC, S	Death	No
29–42. (8)	See description below‡		aPL+		NR	Recovery (5)	NR
43. (35)	Cutaneous T-cell lymphoma	CVA, skin thrombosis	LA, aCL IgG (212 GPL)		S, Cyclo, Ch	Recovery	No
44. (36)	Splenic lymphoma	AHA	LA, aCL IgM	AHA	Ch, Splenectomy	Recovery	Yes
45. (37)	Ovarian adenocarcinoma	DVT, PE, VL, IVC	LA, aCL IgM (28 U)		AC, Ch, S, AZA Thrombectomy	Recovery	Yes
46. (38)	Acute monocytic leukemia	Tibial artery thromb CVA, thrombocytop	LA, aCL IgG (25 GPL)	PAPS	AC, Ch	Death	No
47. (39)	Extensive melanoma		LA, aCL IgG (38 U)		Interferon-α 2b	Recovery	NR
48. (39)	Extensive melanoma	DVT	LA, aCL IgG (40 U)		Interferon-α 2b	Recovery	NR
49. (39)	Extensive melanoma	DVT	LA, aCL IgG (80 U)		Interferon-α 2b, IL-2	Recovery	NR

Table 3 (continued)

Case (Ref.)	Neoplasm	Features Suggestive of APS	aPL†	Related Autoinmune Disease	Treatment	Outcome	Remission of the aPL*
50. (39)	Limited melanoma	DVT	LA, aCL IgG		Interferon-α 2b, IL-2	Recovery	NR
51. (39)	Limited melanoma	PE	LA, aCL IgG		Interferon-α 2b, IL-2	Recovery	NR
52. (40)	Cutaneous T-cell lymphoma	Thrombocytop	LA, aCL IgG (93 GPL)		Ch	Recovery	No
53. (41)	Lung adenocarcinoma	VL, DVT, CVA, Pulmonar, adrenal Cardiac, splenic, renal	LA, aCL IgG (25 GPL)	CAPS	AC, S	Death	No
54. (42)	Limited melanoma	CVA, SA	aPL+			Recovery	NR
55. (43)	NHL	Retinal, bone, splenic TMA	LA	CAPS	S, P, HD, Ch	Death	Yes
56. (44)	Chronic myelomonocytic leukemia	Splenic, aortic, renal Leg arterial thrombosis	aCL IgG (112 GPL)	CAPS	AC, prostaglandin	Recovery	NR
57. (45)	Peripheral T-cell lymphoma	CVA, TIA, DVT, PE Renal	LA, aCL IgM (22 U)		AC, Ch	Recovery	NR
58. (46)	NHL	Thrombocytop	LA		Splenectomy	Recovery	Yes
59. (47)	Chronic myelomonocytic leukemia	TIA, thrombocytop	LA	PAPS	S	Recovery	No
60. (48)	Splenic marginal zone lymphoma	Thrombocytop	LA	Evans syndrome	S, splenectomy, Ch Irrad	Recovery	Yes
61. (48)	Splenic marginal zone lymphoma	AHA	LA, aCL IgM	AHA	Ch, splenectomy	Recovery	Yes
62. (49)	Hairy cell leukemia	AHA, skin ulcers	aPL+	PAPS	AC, Interferon Splenectomy	Recovery	NR
63. (50)	Renal cell carcinoma	Mesenteric vein	aCL IgG	CAPS Scleroderma	Nephrectomy	Recovery	Yes
64. (51)	Angiocentric lymphoma	PH, VL, adrenal, splenic, CVA, RF	LA, aCL IgG (high)		S, Cyclo	Death	No
65. (52)	Mesothelioma	LR, skin ulcer	LA, aCL IgM (12 U)		AC, S	Death	No
66. (53)	B-cell lymphoma	BMN, thrombocytop	aCL IgG (>100 U)		Ch	Death	No
67. (54)	Tracheal carcinoma	Thrombocytop, PE	aCL		S, IVIG	Death	NR
68. (55)	NHL	DVT, thrombocytop	LA, aCL IgG (high), IgM (high), B2GP1	PAPS	AC	Recovery	No
69. (56)	Gastric carcinoma	DVT, CVA, VL Renal, splenic Pulmonary infarct	aCL IgM	PAPS, CAPS	S, P	Death	NR
70. (57)	Light-chain multiple myeloma	DVT	LA	PAPS	NR	NR	NR
71. (58)	Lung squamous cell carcinoma	Adrenal, VL	LA, aCL IgG (50 GPL)	PAPS	CH, Irrad	Death	NR
72. (59)	Carcinoma with primary unknown	CVA, VL, ARDS Retinal vein, renal	LA, aCL IgG (high)	PAPS, CAPS	AC	Death	No
73. (60)	B-cell lymphoma		LA, aCL IgG	Lupus-like	Ch, Irrad	Recovery	No
74. (61)	Lung adenocarcinoma	CVA, hepatic, intestinal	LA	PAPS,	Irrad, surgery CAPS	Death	No
75. (62)	Cholangiocarcinoma	DVT, PE, foot gangrene	LA	PAPS	AC, Vena cava filter	Death	No
76. (63)	Basal ganglia germinoma	CVA	aCL IgG (72U)		Irrad	Recovery	No
77. (64)	Uterine carcinoma	CVA, MI, VL, renal Splenic, pancreatic	LA, aCL IgG, (227 U) aCL	SLE, CAPS	S, Cyclo	Death	No
	Digital necrosis	IgM (5.9 U)					

Table 3 (continued)

Case (Ref.)	Neoplasm	Features Suggestive of APS	aPL†	Related Autoinmune Disease	Treatment	Outcome	Remission of the aPL*
78. (65)	Chronic myeloid leukemia	Hepatic veno-occlusive	LA		BMT, S, CsA, Cyclo Irrad	Recovery	Yes
79. (66)	Chronic B-cell lymphocytic leukemia	DVT, PE, Thrombocytop	LA, aCL IgG (265 GPL) IgM (3880 MPL)		AC, S, Ch	Death	No
80. (67)	Breast carcinoma	DVT, PE	LA	AC		Recovery	NR
81. (68)	Chronic myeloid leukemia	TMA, MI	aCL IgG (331 GPL)		AC, interferon α	Death	NR
82. (69)	Lung adenocarcinoma	DVT, foot gangrene	aCL IgG (27 GPL), IgM (67 MPL)		AC, Ch	Death	NR
83. (70)	Chronic myelomonocytic leukemia	PE, splenic	LA		AC, splenectomy	Death	No
84. (71)	Lung adenocarcinoma	CVA, splenic, renal Pulmonary infarct	LA	PAPS, CAPS	AC, S	Death	No
85. (72)	Lung adenocarcinoma	CVA, PE, renal mesenteric, skin ulcers	LA, aCL IgG	PAPS, CAPS	AC, S	Death	No
86. (73)	Splenic marginal zone NHL	PE	LA, aCL IgG, IgM, B2GP1	PAPS	Ch, Rituximab	Recovery	Yes
87. (74)	B-cell follicle center lymphoma	Retinal arterial thromb.	aCL IgG (85 U), IgM (128 U) B2GP1	Lupus-like	AC, Ch	Recovery	No
88. (75)	Low-grade B-cell lymphoma	CVA	aCL IgM (529 U)		ASA	Recovery	NR
89. (75)	Breast carcinoma	DVT	aCL IgG (30.1)		NR	NR	NR
90. (75)	Pharyngeal carcinoma	Sup. vein thrombosis	aCL IgG (34.5)		NR	NR	NR
91. (75)	Parotid carcinoma	DVT	aCL IgG (15.6)		NR	NR	NR
92. (75)	Carcinoma with primary unknown	CVA	aCL IgG (20.3)		NR	NR	NR
93. (75)	Breast carcinoma	PE	aCL IgG (22.0)		Surgery	Death	No
94. (75)	Carcinoma with primary unknown		aCL IgG (20.8)		NR	NR	NR
95. (76)	Carcinoid tumor	SA, mesenteric, pancreas, thrombocytop porta thrombosis	aCL IgG	PAPS	AC, Duodeno-pancreactectomy	Recovery	NR
96. (77)	Hodgkin disease	MI	aCL IgG (high)		AC	Recovery	No
97. (77)	B-cell lymphoma	CVA, VL, thrombocytop	LA, aCL IgG		Ch	Recovery	Yes
98. (77)	Cutaneous and ganglionar B-cell lymphoma Breast carcinoma	DVT	LA, aCL IgG	AHA	AC, S, Cyclo Splenectomy	Recovery	No
99. (77)	B-cell lymphoma Renal cell carcinoma Papillany thyroid carcinoma	Thombocytop, CVA, LR	LA, aCL IgG B2GP1 B2GP1	Sneddon's syndrome	ASA, S, danazol Nephrectomy Thyroidectomy	Recovery	No
100. (78)	B-cell lymphoma	Skin thrombosis	aCL IgG (39 U)		S, Ch, Irrad	Recovery	Yes
101. (79)	Myeloproliferative syndrome	Portal, splenic	LA, aCL IgG (31U)		AC	Recovery	NR
102. (80)	Diffuse large B-cell lymphoma		LA	Lupus-like	Ch	Recovery	NR
103. (81)	NHL	Recurrent arterial	LA	Sarcoidosis	AC, S, thrombolysis Ch, amputation	Recovery	No
104. (82)	Chronic myelogenous leukemia	Bilateral retinal vein	aCL IgM (22 U)		Interferon	Recovery	NR
105. (83)	Multiple myeloma		LA		NR	NR	NR
106. (84)	Carcinoma with primary unknown	CVA, PE, MI Digital necrosis	aCL IgG (32 GPL)	PAPS, CAPS	AC, S, P	Recovery	NR
107. (85)	Non-small-cell lung carcinoma	LR, digital ischemia Thrombocytop	LA, aCL IgG (53.8 GPL)	Lupus-like	ASA, P, Rad, Ch Lobectomy	Death	No

Table 3 (continued)

Case (Ref.)	Neoplasm	Features Suggestive of APS	aPL†	Related Autoinmune Disease	Treatment	Outcome	Remission of the aPL*
108. (86)	Cholangiocarcinoma	DVT, CVA, hepatic	aCL IgG	U. Colitis, CAPS	AC, S, Cyclo	Recovery	NR
109. (86)	Lymphoma	Renal, mesenteric MI, digital necrosis Intestinal	LA, aCL IgG	Lupus-like, CAPS	AC, S, Cyclo, P	Death	NR
110. (87)	Leiomyosarcoma	DVT, PE, IVC, renal Hepatic, thrombocytop	LA, aCL IgG (high), B2GP1	PAPS, CAPS	AC, S, Cyclo, P, Thrombolysis, IVIG	Death	No
111. (88)	Renal cell carcinoma		LA		Nephrectomy	Recovery	Yes
112. (89)	Lymphoplasmacytoid lymphoma	Thrombocytop	LA, aCL IgM (420 MPL)		Ch, splenectomy	Death	No
113. (90)	Breast carcinoma	CVA, DVT, PE, VL LR, leg ulcer, LR, leg ulcer,	LA, aCL IgG (377.2) IgA (19.2) IgG (377.2) IgA (19.2)	SLE, CAPS	AC,Ch, S, Cyclo, AZA	Recovery	NR
114. (90)	Colon adenocarcinoma	Subclavian thromb. PE, IVC, VL, RF, CVA	LA, aCL IgM (19.1)	CAPS	AC, ASA	Recovery	Yes
115. (91)	Adenocarcinoma with primary unknown	CVA, DVT, PE	LA, aCL IgG (21.4 GPL)	PAPS	AC	Death	No
116. (92)	Renal cell carcinoma	MI, stent thrombosis	LA, aCL+	PAPS	AC, thrombolysis, ASA Clopidrogel, abciximab Nephrectomy	Recovery	NR
117. (93)	NHL	Skin ulcers	LA, aCL IgG (92 GPL)	Cryoglobulinemia	AC, S, Ch	Recovery	No
118. (94)	Meningioma	TMA, LR, ARDS Thrombocytop	LA	PAPS, CAPS	AC, P, HD Tumor resection	Recovery	No
119. (95)	Hodgkin's lymphoma	CVA	LA	PAPS	Ch	Recovery	NR
120. (96)	Acute myeloblastic leukemia	SA, IVC thrombosis	aCL IgG (34 GPL)	PAPS	AC, S	Death	No

AC, anticoagulation; aCL, anticardiolipin antibodies; aPL, antiphospholipid antibodies; AZA, azathioprine; BMN, bone marrow necrosis; BMT, bone marrow transplantation; CAPS, catastrophic antiphospholipid syndrome; Ch, chemotherapy; CVA, cerebrovascular accident; CsA, cyclosporine; Cyclo, cyclophos phamide; DVT, deep vein thrombosis; FFP, fresh frozen plasma; HD, hemodialysis; IL-2, interleukin 2; Irrad, irradiation; IVC, inferior vena cava; LA, lupus anticoagulant; LR, livedo reticularis; NHL, non-Hodgkin's lymphoma, NR, not reported; PAPS, primary antiphospholipid syndrome; PE, pulmonary embolism; PH, pulmonary hemorrhage; RF, renal failure; SA, spontaneous abortion; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; TMA, thrombotic microangiopathy; thrombocytop: thrombocytopenia; VL, valve lesion.

*aPL negative after neoplasm therapy.

†aPL titers are shown in available cases.

‡Schved et al (8) (No. cases): Prostatic carcinoma (3), breast carcinoma (2), carcinoma with primary unknown (2), NHL (1), ovarian carcinoma (1), hepatocarcinoma (1), pulmonary epithelioma (1), colon adenocarcinoma (1), cutaneous sqamous-cell carcinoma (1), oropharyngeal carcinoma (1).

disturbances (increased amounts of von Willebrand factor and thrombomodulin), abnormalities of blood flow (high viscosity), an increase of inflammatory cytokines [tumor necrosis factor (TNF) and interleukin-1] and abnormal tumor angiogenesis (100). Other genetic causes of thrombophilia, such as factor V Leiden and the prothrombin gene mutation, have not been specifically associated with thrombosis in patients with cancer (2).

Thromboembolic episodes are not uncommon in some solid tumors (eg, brain, pancreatic, lung, breast, ovary, renal, etc), although the prevalence in hematologic malignancies is lower than that reported for solid tumors, and the number of thrombotic events are increasingly being reported in patients with acute leukemia, and chronic myeloproliferative and lymphoproliferative disorders.

Before the standardization of aCL and the description of the APS (101), some malignancies were described in association with the presence of a BFP-STS and LA (12-16). In 1976, Schleider and coworkers (102) studied 83 patients with circulant anticoagulants and found that, among 58 patients with LA, 8 had oncologic processes, including multiple myeloma, Hodgkin's disease, prostatic carcinoma, myelofibrosis, cervical carcinoma, cecal carcinoma, metastatic adenocarcinoma, and lymphosarcoma. Later, other associations have been described with aPL antibodies and not only with aCL, LA, or β2-GPI, but also with antibodies against phos-

phatidylinositol (103), phosphatidylserine, phosphatidyletholamine, phosphatidylcholine, and phosphatidylglycerol (104); however, these antibodies are not used routinely in the diagnosis of APS.

Although the aPL could be "innocent bystanders" in thrombosis associated with malignancies, several studies have suggested some clinical implications derived from this association. Zuckerman and coworkers (6) performed a case-controlled study including 216 patients with solid and non-solid malignancies and 88 age-matched healthy subjects. They found that 47 (22%) patients with malignancies were aCL positive, compared with only 3 in the control group. Of the 47 patients, 31 had IgG aCL, 7 had IgM aCL, and 9 had both. The aCL-positive patients (13/47) had a significantly higher rate of thromboembolic events than those patients without aCL (24/169). Interestingly, the levels of aCL decreased after successful treatment in 4 patients (2 with colon cancer, 1 with lung cancer, and 1 with NHL) and they remained free of thrombotic events.

A large prospective epidemiological study on the occurrence of aPL was conducted in Montpelier, France, by Schved and coworkers (8); 1014 patients were tested at entry. Seventy-two (7%) patients were positive at least once for aPL. Cancer was recorded in 14 of these patients: 9 had an active malignant disease and 5 had cancer in their past history.

Stasi and coworkers (9) studied the prevalence of aPL and their correlation with cytokine levels in a small group of patients with AML (19 patients) and NHL (14 patients). Among patients with AML, 5 (26%) patients had LA and/or aCL at diagnosis. One of them achieved complete remission with disappearance of LA, while in 3 cases the LA and 1 in case the aCL persisted positive. Among patients with NHL, 5 (35%) patients had LA and 1 had aCL at diagnosis, and all cases became negative for LA and aCL after cancer treatment. Additionally, the authors found a correlation between the concentrations of interleukin-6 and TNF-alpha and IgG aCL during different determinations.

In another study in patients with AML (11), the authors found positive aCL titers in 25 (68%) of 37 patients included. In those patients with response to chemotherapy, aCL titers fell (especially IgM aCL); however, AML relapses were accompanied by reappearance of aCL. In 5 patients with chemoresistant AML, aCL were persistently positive. aCL correlate also with AML activity in the majority of patients. The authors suggested that serum aCL may be a useful marker for the assessment of relapses, disease activity, and therapy response.

Until now, there are limited data to determine if patients with primary APS have an increased risk of developing cancer as occurs in other systemic autoimmune diseases (eg, SLE, Sjögren's syndrome, rheumatoid arthritis, or dermatomyositis) (69, 105). In a cohort of Italian patients, Finazzi and coworkers (106) studied, in a prospective manner, 360 patients with aPL. They reported that after 4 years of follow-up, 4 patients with primary APS developed a malignant disease (1 breast carcinoma and 3 NHL), resulting an estimated rate of 0.28% patient/year, by far a higher incidence for NHL than its incidence in the Western population. Although these data are not conclusive, it is important to bear in mind the possibility of an underlying malignancy in patients with atypical presentation of APS (specially elderly patients). In the present series, 54 patients were older than 60 years, with a mean age of 56 ± 42 years (range, 5 to 78 years), a considerably higher mean age than the "classical" form of presentation of APS (42 ± 14 years) (3).

In general, thromboembolic events in patients with cancer do not differ clinically from those in other types of prothrombotic states. As in the present series, the main clinical manifestations are DVT, PE, and CVA; however, we found unusual thrombotic presentations, such as bone marrow necrosis, chorea, or bone infarct. Furthermore, we found 17 cases of catastrophic APS associated with malignancies.

In the APS associated with autoimmune diseases or chronic infections, aPL titers wax and wane throughout time, but usually do not disappear. This situation seems different in the APS associated with cancer, where, in an important number of patients, aPL disappear after a proper treatment against the malignancy.

In patients with aPL and cancer, long-term anticoagulation seems necessary. Nonetheless, in those patients with the disease under control and the disappearance of aPL, anticoagulation could be stopped or could be replaced by antiaggregation. Thromboprophylaxis is important in cancer patients (even more if they have aPL), especially for high-risk situations such as surgery, catheter implantation, and chemotherapy. Recently, an increase in thromboembolic risk has been described with the use of new anticancer drugs, such as antiangiogenic agents and matrix metalloproteinase inhibitors (107). Additionally, immunotherapies, such as interferon and interleukin-2, can induce aPL (5).

In conclusion, the aPL are associated with a wide variety of malignancies, mainly B-cell lymphoma, splenic lymphoma, chronic myeloid lymphoma, renal cell carcinoma, NHL, and lung adenocarcinoma. In some cases, the malignancy can trigger a life-threatening form of APS presentation (catastrophic APS). aPL remitted in more than one-third of patients after cancer treatment. Furthermore, it is important to bear in mind, especially in elderly patients, that thrombotic events associated with aPL can be the first manifestation of malignancy.

References

1. Trousseau A. Phlegmasia alba dolens Clinique Medical de L'Hotel-Dieu de Paris, Vol. 3. The New Sydenham Society, London, 1865; p 94.
2. Lee AY, Levine MN. Venous thromboembolism and cancer: risks and outcomes. Circulation 2003;107:I17-21.
3. Cervera R, Piette JC, Font J, Khamashta MA, Shoenfeld Y, Camps MT, et al. Antiphospholipid syndrome: Clinical and immunological manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthritis Rheum 2002;46:1019-27.
4. Cervera R, Asherson RA, Acevedo ML, Gómez-Puerta JA, Espinosa G, De La Red G, et al. Antiphospholipid syndrome triggered by infections: a report of two cases and a review of clinical presentations in 100 patients. Ann Rheum Dis 2004;63:1312-7.
5. Asherson RA, Cervera R. Antiphospholipid antibodies and malignancies. In: Shoenfeld Y, ed. Cancer and Autoimmunity. Elsevier, Amsterdam, 2000;93-102.

6. Zuckerman E, Toubi E, Golan TD, Rosenvald-Zuckerman T, Sabo E, Shmuel Z, et al. Increased thromboembolic incidence in anti-cardiolipin-positive patients with malignancy. Br J Cancer 1995;72:447-51.
7. Borche L, Lim A, Binet JL, Dighiero G. Evidence that chronic lymphocytic leukemia B lymphocytes are frequently committed to production of natural autoantibodies. Blood 1990;76:562-9.
8. Schved JF, Dupuy-Fons C, Biron C, Quere I, Janbon C. A prospective epidemiological study on the occurrence of antiphospholipid antibody: the Montpellier Antiphospholipid (MAP) Study. Haemostasis 1994;24:175-82.
9. Stasi R, Stipa E, Masi M, Oliva F, Sciarra A, Perrotti A, et al. Antiphospholipid antibodies: prevalence, clinical significance and correlation to cytokine levels in acute myeloid leukemia and non-Hodgkin's lymphoma. Thromb Haemost 1993;70:568-72.
10. Stern JJ, Ng RH, Triplett DA, McIntyre JA. Incidence of antiphospholipid antibodies in patients with monoclonal gammopathy of undetermined significance. Am J Clin Pathol 1994;101:471-4.
11. Lossos IS, Bogomolski-Yahalom V, Matzner Y. Anticardiolipin antibodies in acute myeloid leukemia: prevalence and clinical significance. Am J Hematol 1998;57:139-43.
12. Wuepper KD, Tuffanelli DL. False-positive reaction to VRDL test with prozone phenomena. Association with lymphosarcoma. JAMA 1966; 195:180-1.
13. Cooper MR, Cohen HJ, Huntley CC, Waite BM, Spees L, Spurr CL. A monoclonal IgM with antibody specificity for phospholipids in a patient with lymphoma. Blood 1974;43:493-501.
14. Drusin LM, Litwin SD, Armstrong D, Webster BP. Waldeström macroglobulinemia in a patient with a chronic biologic false-positive serologic test for syphilis. Am J Med 1974;56:429-32.
15. Marcus R, Grayzel A. A lupus antibody syndrome associated with hypernephroma. Arthritis Rheum 1979;22:1396-8.
16. Andes WA. IgM anticoagulant with acquired abormalities in factor VIII. Thromb Res 1982;27:703-12.
17. Richard C, Sedano MC, Mazorra F, Recio M, Cuadrado MA, Bello C, et al. Hairy-cell leukaemia associated with auto-immune disorders in the form of a 'lupus-type' anticoagulant and a positive direct Coombs' test. Acta Haematol 1986;75:181-2.
18. Kozlowski CL, Johnson MJ, Gorst DW, Willey RF. Lung cancer, immune thrombocytopenia and the lupus inhibitor. Postgrad Med J 1987;63:793-5.
19. Levine SR, Diaczok IM, Deegan MJ, Kieran SN, Feit H, Elias SB, et al. Recurrent stroke associated with thymoma and anticardiolipin antibodies. Arch Neurol 1987;44:678-9.
20. Duncombe AS, Dalton RG, Savidge GF. Lupus-type coagulation inhibitor in hairy cell leukaemia and resolution with splenectomy. Br J Haematol 1987;65:120-1.
21. Allegue F, Martin Gonzalez M, Alonso ML, Garcia Larana J, Moreno R, Ledo A. Antiphospholipid syndrome in a patient with T-cell skin lymphoma. Med Cutan Ibero Lat Am 1989;17:49-51.
22. Zuber M, Gherardi R, Defer G, Gaulard P, Divine M, Zafrani ES. Peripheral neuropathy, coagulopathy and nodular regenerative hyperplasia of the liver in a patient with multiple serologic auto-antibody activities and IgM B-cell lymphoma. J Intern Med 1989;226:291-5.
23. Bellotti V, Gamba G, Merlini G, Montani N, Bucciarelli E, Stoppini M, et al. Study of three patients with monoclonal gammopathies and 'lupus-like' anticoagulants. Br J Haematol 1989;73:221-7.
24. Makar AP, Vanderheyden JS, Verheyen A. Maternal and fetal complications associating lupus anticoagulant and its management; three case reports. Eur J Obstet Gynecol Reprod Biol 1990;36:185-95.
25. Meyrier A, Becquemont L, Weill B, Callard P, Rainfray M. Hemolytic-uremic syndrome with anticardiolipin antibodies revealing paraneoplastic systemic scleroderma. Nephron 1991;59:493-6.
26. Morio S, Oh H, Hirasawa A, Aotsuka N, Nakamura H, Asai T, et al. Hepatic veno-occlusive disease in a patient with lupus anticoagulant after allogeic bone marrow transplantation. Bone Marrow Transplant 1991;8:147-9.
27. Schirren CG, Schlag R, Eckert F, Spann W, Meurer M, Kaudewitz P, et al. Multilocular, immature-cell myelogenous infiltrates of the skin in a patient with chronic myelomonocytic luekemia following polycitemia vera and anti-cardiolipin syndrome. Hautarzt 1991;42:258-62.
28. Ciaudo M, Horellou MH, Audouin J, De Carbonnieres C, Conard J, Samama M. Lupus anticoagulant associated with primary malignant lymphoplasmacytic lymphoma of the spleen: A report of four cases. Am J Hematol 1991;38:271-6.
29. Asherson RA, Block S, Houssiau FA, Hughes GR. Systemic lupus erythematosus and lymphoma: association with antiphospholipid syndrome. J Rheumatol 1991;18:277-9.
30. Schiff DE, Ortega JA. Chorea, eosinophilia, and lupus anticoagulant associated with acute lymphoblastic leukemia. Pediatr Neurol 1992; 8:466-8.
31. Arruda VR, Bizzacchi JM, Metze IL. Hairy cell leukemia and multiple autoimmune manifestations in a human immunodeficiency virus-infected patient. Ann Hematol 1993;66:325-7.
32. Malnick S, Sthoeger Z, Attali M, Geltner D. Anticardiolipin antibodies associated with hypernephroma. Eur J Med 1993;2:308-9.
33. Fautrel B, Cherin P, Tertian G, Brivet F, Naveau S, Sedel D, et al. Chronic lymphoid leukemia, leiomyoblastoma, thrombosing vasculitis and anticardiolipin antibodies: apropos of a case. Rev Med Interne 1993;14:171-3.
34. Papagannis A, Cooper A, Banks J. Pulmonary embolism and lupus anticoagulant in a woman with renal cell carcinoma. J Urol 1994;152: 941-2.
35. Hill VA, Whittaker SJ, Hunt BJ, Liddell K, Spittle MF, Smith NP. Cutaneous necrosis associated with the antiphospholipid syndrome and mycosis fungoides. Br J Dermatol 1994;130:92-6.
36. Sawamura M, Yamaguchi S, Murakami H, Amagai H, Matsushima T, Tamura J, et al. Multiple autoantibody production in a patient with splenic lymphoma. Ann Hematol 1994;68:251-4; J Rheumatol 1994; 21:2162-3.
37. Ruffatti A, Aversa S, Del Ross T, Tonetto S, Fiorentino M. Antiphospholipid antibody syndrome associated with ovarian cancer. A new paraneoplastic syndrome? J Rheumatol 1994;21:2162-3.
38. Mouas H, Lortholary O, Eclache V, Leroux G, Casassus P, Guillevin L, et al. Antiphospholipid syndrome during acute monocytic leukaemia. Eur J Haematol 1994;53:59-60.
39. Becker JC, Winkler B, Klingert S, Bröker EB. Antiphospholipid syndrome associated with immunotherapy for patients with melanoma. Cancer 1994;73:1621-4.
40. Carrascosa M, Hernandez IJ, Perez-Castrillon JL, Sampedro J. Antiphospholipid antibodies and Sezary syndrome (letter). Am J Haematol 1995;49:365.
41. Bessis D, Sotto A, Viard JP, Berard M, Ciurana AJ, Boffa MC. Trousseau's syndrome with nonbacterial thrombotic endocarditis: pathogenic role of antiphospholipid syndrome. Am J Med 1995;98:511-3.
42. Naldi L, Locati F, Finazzi G, Barbui T, Cainelli T. Antiphospholipid syndrome associated with immunotherapy for patients with melanoma. Cancer 1995;75:2784-5.
43. Keung YK, Cobos E, Meyerrose GE, Roberson GH. Progressive thrombosis after treatment of diffuse large cell non-Hodgkin's lymphoma and concomitant lupus anticoagulant. Leuk Lymphoma 1996; 20:341-5.
44. Messiaen T, Lefebvre C, Lambert M. Case report: thoracic aorta thrombus with systemic embolization: a rare paraneoplastic antiphospholipid syndrome? Am J Med Sci 1996;312:303-5.
45. Onida P, Tresoldi M, Rugarli C. Anti-phospholipid-antibody syndrome associated with peripheral T-cell lymphoma. Am J Hematol 1997;55:167-8.
46. McGuire D, Zeidman A, Mittelman M. Non-Hodgkin's lymphoma presenting with coagulopathy due to anti-phospholipid antibody syndrome. Leuk Lymphoma 1997;26:193-6.
47. Yahata N, Ohyashiki K, Iwama H, Katagiri T, Kodama S, Tauchi T, et al. Chronic myelomonocytic leukemia in a patient with antiphospholipid syndrome: first case report. Leuk Res 1997;21:889-90.
48. Murayami H, Irisawa H, Saitoh T, Matsushima T, Tamura J, Sawamura M, et al. Immunological abnormalities in splenic marginal zone cell lymphoma. Am J Hematol 1997;56:173-8.
49. Amato S, Gaeta G, Brancaccio V, Belfiore G. Primary antiphospholipid

antibody syndrome with left atrial intracardiac thombosis. G Ital Cardiol 1997;27:380-6.
50. Sanchez-Ortiz RF, Fraker DL, Malkowicz SB. Renal cell carcinoma presenting with mesenteric thrombosis and anticardiolipin antibodies: echoes of Trousseau's syndrome? J Urol 1998;159:2078.
51. Lago H, Grinberg A. Esclerodermia lineal, aborto espontáneo y hemiplejía; hemorragia pulmonar, anticuerpos antifosfolipídicos y linfoma angiocéntrico. Medicina (B Aires) 1998;58:67-77.
52. Tucker SC, Coulson IH, Salman W, Kendra JR, Johnson CE. Mesothelioma-associated antiphospholipid antibody syndrome presenting with cutaneous infarction and neuropathy. Br J Dermatol 1998;138: 1092-4.
53. Murphy PT, Sivakumaran M, Casey MC, Liddicoat A, Wood JK. Lymphoma associated bone marrow necrosis with raised anticardiolipin antibody. J Clin Pathol 1998;51:407-9.
54. Hofgartner F, Bader A, Burkle V, Schmeiser T, Bosch A, Sigel H. Right ventricular thrombus after pacemaker implantation in a patient with secondary antiphospholipid syndrome. Dtsch Med Wochenschr 1998;123:12-6.
55. Brohee D, Delval L, Cauchie P. CD4 lymphocyte deficiency and non-Hodgkin's lymphoma in the antiphospholipid syndrome. Ann Oncol 1998;9:921.
56. Soltesz P, Szekanecz Z, Vegh J, Lakos G, Toth L, Szakall S, et al. Catastrophic antiphospholipid antibody syndrome in a cancer patient. Orv Hetil 1999;140:2917-20.
57. Yasin Z, Quick D, Thiagarajan P, Spoor D, Caraveo J, Palascak J. Light-chain paraproteins with lupus anticoagulant activity. Am J Hematol 1999;62:99-102.
58. Jullien V, Heudier P, Carre Y, Peyrade F, Taillan B, Tchiknavorian X, et al. Bronchopulmonary cancer, antiphospholipid syndrome and coagulation disorders. Rev Med Interne 1999;20:696-700.
59. Piette JC, Amoura Z, Foucher-Lavergne A. "Catastrophic" diagnosis of the antiphospholipid syndrome. Ann Intern Med 1999;131:798-9.
60. Stefani PM, Pietrogrande F, Sartori R, Girolami A. Immunosuppression due to MACOP-B does not seem to cure the antiphospholipid syndrome. Haematologica 1999;84:751-2.
61. Yoshida J, Iwai T, Mayumi T, Ekimura M, Ikeda S, Matsuo K, et al. A patient operated for occlusion of the superior mesenteric artery. Nippon Geka Gakkai Zasshi 1999;100:228-30.
62. Samadian S, Estcourt L. Recurrent thrombo-embolic episodes: the association of cholangiocarcinoma with antiphospholipid syndrome. Postgrad Med J 1999;75:45-6.
63. Liu E, Robertson RL, du Plessis A, Pomeroy SL. Basal ganglia germinoma with progressive cerebral hemiatrophy. Pediatr Neurol 1999; 20:312-4.
64. Grinberg AR, Heller PG, Correa G, Sarano JF, Molinas FC, Nicastro MA, et al. Síndrome antifosfolipido catastrófico: Comunicación de dos formas de presentación. Medicina (Buenos Aires) 1999;59:743-6.
65. Olalla JI, Ortín M, Hermida G, Baro J, Sedano C, Morante C, et al. Disappearance of lupus anticoagulant after allogeneic bone marrow transplantation. Bone Marrow Transplant 1999;23:83-5.
66. Ghirarduzzi A, Silingardi M, D'Inca M, Tincani E. Sindrome da anticorpi antifosfolipidi in corso di leucemia linfatica cronica. Associazione con autoanticorpi anti-fattore VIII. Ann Ital Med Int 1999;14: 436-50.
67. Ootaki C, Uchida T, Matsutani R, Fukunaga H. A case of intraoperative pulmonary embolism associated with lupus anticoagulant. Masui 2000;49:1109-14.
68. Magee CC, Abraham K, Farrell J, Dorman T, Walshe JJ. Renal thrombotic microangiopathy associated with interferon-alpha treatment of chronic myeloid leukemia. Am J Kidney Dis 2000;36(E5):1-5.
69. Yang MH, Fan FS, Chen PM, Liu JH, Chiou TJ, Wang WS, et al. Venous gangrene in a patient with adenocarcinoma of the lung. Jpn J Clin Oncol 2000;30:276-8.
70. Viallard JF, Marit G, Reiffers J, Broustet A, Parrens M. Antiphospholipid syndrome during chronic myelomonocytic leukemia. Am J Haematol 2000;63:60.
71. Katsuoka H, Mimori Y, Kohriyama T, Higaki M, Mitsuoka T, Harada A, et al. An autopsy case of catastrophic antiphospholipid syndrome presenting with recurrent multiple cerebral infarction associated with lung cancer. No To Shinkei 2000;52:64-9.
72. Yahamoto T, Ito M, Nagata S, Suzuki H, Togawa A, Nagase M, et al. Catastrophic exacerbation of the antiphospholipid syndrome after a lung adenocarcinoma biopsy. J Rheumatol 2000;27:2035-37.
73. Vacca A, Littera R, Carta M. APS syndrome in a patient with non-Hodgkin's lymphoma of the marginal zone: effectiveness of chemoimmunotherapy with fludarabina and rituximab. J Autoimmunol 2000;15:77 (abstract).
74. Genvresse I, Buttgereit F, Spath-Schwalbe E, Ziemer S, Eucker J, Possinger K. Arterial thrombosis associated with anticardiolipin and anti-beta2-glycoprotein-I antibodies in patients with non-Hodgkin's lymphoma: a report of two cases. Eur J Haematol 2000;65:344-7.
75. Armas JB, Dantas J, Mendonca D, Farto R, Ribeiro M, Herrero-Beaumont G, et al. Anticardiolipin and antinuclear antibodies in cancer patients—a case control study. Clin Exp Rheumatol 2000;18:227-32.
76. Aranguren A, Perez-Salazar M, Paramo JA, Zozaya J, Rocha E. Antiphospholipid antibodies, portal and mesenteric thrombosis and carcinoid tumor: a case report. Thromb Haemost 2001;86:1334.
77. Liozon E, Loustaud V, Jauberteau MO, Jaccard A, Soria P, Bordessoule D, et al. Non-synchronous malignant lymphoma and antiphospholipid syndrome: report of four cases. Rev Med Interne 2001;22:360-70.
78. Esteve E, Maitre F, Legac E. Purpura vasculaire au cours d'une gale sévère. Ann Dermatol Venereol 2001;128:11-4.
79. Diaz E, Nahon S, Charachon A, Traissac L, Lenoble M, Challier E, et al. Portal vein thrombosis associated with a myeloproliferative disorder, prothrombin G20210A mutation, antiphospholipid syndrome, with repermeation during anticoagulant therapy. Gastroenterol Clin Biol 2001;25:549-51.
80. Campbell J, Miles H, Juneja SK, Seymour JF, Slavin M. Diffuse large cell lymphoma and t(8;22) (q24;q11) in a patient with idiopathic CD4+ T-lymphopenia. Leuk Lymphoma 2001;41:421-3.
81. Shaw BE, Perry D, Hoffbrand V. Progressive arterial thrombosis in a patient with non-Hodgkin's lymphoma, a lupus anticoagulant, factor V leiden mutation and paraprotein, following chemotherapy. Leuk Lymphoma 2001;42:221-3.
82. Al-Abdulla NA, Thompson JT, LaBorwit SE. Simultaneous bilateral central retinal vein occlusion associated with anticardiolipin antibodies in leukemia. Am J Ophthalmol 2001;132:266-8.
83. Shinagawa A, Kojima H, Kobayashi T, Kawada K, Nagasawa T. Lupus anticoagulant-like activity observed in a dimeric lambda protein produced by myeloma cells. Int J Hematol 2001;73:526-31.
84. Flores D, Galarza DA, Esquivel JA, Garza M. Carcinoma epitelial metastásico a médula ósea con primario desconocido asociado a manifestaciones clínicas de síndrome antifosfolípido. Presentación de un caso clínico. Rev Mex Reumat 2001;16:349-53.
85. Vaidya S, Logan JW. Anti-cardiolipin antibodies, Raynaud's phenomenon with digital ischemia, and non small cell carcinoma of the lung. Scand J Rheumatol 2001;30:172-4.
86. Asherson R Cervera R, Piette JC, Shoenfeld Y, Espinosa G, Petri MA, et al. Catastrophic antiphospholipid syndrome. Clues to the pathogenesis from a series of 80 patients. Medicine 2001;80:355-77.
87. Espiritu JD, Creer MH, Miklos AZ, Bajaj MS. Fatal tumor thrombosis due to an inferior vena cava leiomyosarcoma in a patient with antiphospholipid antibody syndrome. Mayo Clin Proc 2002;77:595-9.
88. Ather MH, Mithani S, Bhutto S, Adil S. Lupus type anticoagulant in a patient with renal cell carcinoma: an autoimmune paraneoplastic syndrome. J Urol 2002;167:2129.
89. Gallart T, Benito C, Reverter JC, Bosch F, Blay M, Tassies D, et al. True anti-anionic phospholipid immunoglobulin M antibodies can exert lupus anticoagulant activity. Br J Haematol 2002;116:875-6.
90. Langer F, Eifrig B, Marx G, Stork A, Hegewisch-becker S, Hossfeld DK. Exacerbation of antiphospholipid antibody syndrome after treatment of localized cancer: a report of two cases. Ann Hematol 2002; 81:727-31.
91. Kim JS, Choi EJ. Recurrent thromboembolism, adenocarcinoma and antiphospholipid syndrome. Cerebrovasc Dis 2002;14:266-7.
92. Muir DF, Stevens A, Napier-Hemy RO, Fath-Ordoubadi F, Curzen N.

Recurrent stent thrombosis associated with lupus anticoagulant due to renal cell carcinoma. Int J Cardiovasc Intervent 2003;5:44-6.
93. Andrejevic S, Bonaci-Nikolic B, Bukilica M, Milivojevic G, Basanovic J, Nikolic MM. Purpura and leg ulcers in a patient with cryoglobulinemia, non-Hodgkin's lymphoma and antiphospholipid syndrome. Clin Exp Dermatol 2003;28:151-3.
94. Moll Stephan, Kudrik F, Thomas DB. Catastrophic antiphospholipid antibody syndrome. Am J Hematol 2003;72:278-9.
95. Gattorno M, Falcini F, Ravelli A, Zulian F, Buoncompagni A, Martini G, et al. Outcome of primary antiphospholipid syndrome in childhood. Lupus 2003;12:449-53.
96. Saxena SK, Bin Salih SA, Al-Jizeeri AH, Kheir OA. Acute myeloblastic leukemia in a patient with primary antiphospholipid syndrome. Saudi Med J 2003;24:1013-5.
97. Wilson WA, Gharavi AE, Koike T, Lockshin MD, Branch DW, Piette JC, et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. Arthritis Rheum 1999;42:1309-11.
98. Prandoni P, Lensing AWA, Buller HR, Cogo A, Prins MH, Cattelan AM, et al. Deep-vein thrombosis and the incidence of subsequent symptomatic cancer. N Eng J Med 1992;327:1128-33.
99. Rickles FR, Patierno S, Fernandez PM. Tissue factor, thrombin, and cancer. Chest 2003;124:58S-68S.
100. Lip GY, Chin BS, Blann AD. Cancer and the prothrombotic state. Lancet Oncol 2002;3:27-34.
101. Harris EN, Gharavi AE, Boey ML, Patel BM, Mackworth-Young CG, Loizou S, et al. Anticardiolipin antibodies: detection by radioimmunoassay and association with thrombosis in systemic lupus erythematosus. Lancet 1983;2:1211-4.
102. Schleider MA, Nachman RL, Jaffe EA, Coleman M. A clinical study of the lupus anticoagulant. Blood 1976;48:499-509.
103. Falcon CR, Hoffer AM, Carreras LO. Antiphosphatidylinositol antibodies as markers of the antiphospholipid syndrome. Thromb Haemost 1990;63:321-2.
104. Stern JJ, Ng RH, Triplett DA, McIntyre JA. Incidence of antiphospholipid antibodies in patients with monoclonal gammopathy of undetermined significance. Am J Clin Pathol 1994;101:471-4.
105. Naschitz JE, Rosner I, Rozenbaum M, Zuckerman E, Yeshurun D. Rheumatic syndromes: clues to occult neoplasia. Semin Arthritis Rheum 1999;29:43-55.
106. Finazzi G, Brancaccio V, Moia M, Ciaverella N, Mazzucconi MG, Schinco PC, et al. Natural history and risk factors for thrombosis in 360 patients with antiphospholipid antibodies: a four-year prospective study from the Italian Registry. Am J Med 1996;100:530-6.
107. Caine GJ, Lip GY. Thromboembolism associated with new anti-cancer treatment strategies in combination with conventional chemotherapy: new drugs, old risks? Thromb Haemost 2003;90:567-9.

8.2 Summary of results

A total of 120 cases of aPL associated with malignancies were found (62 male and 58 female patients).

- The mean age was 56 years (range, 5 to 88 yr).
- The main hematological malignancies found were B-cell lymphoma in 10 (8%) patients, spleen lymphoma in 8 (7%), and chronic myeloid leukemia in 7 (6%).
- With respect to solid tumors, 7 (6%) patients had renal cell carcinoma, 7 (6%) primary tumor of unknown origin, 6 (5%) lung adenocarcinoma, and 6 (5%) breast carcinoma.
- In 41 cases, the diagnosis of both conditions (APS and cancer) was made simultaneously; in 29 cases, the malignancies were diagnosed after the thrombotic manifestations of APS, and in 25 cases, APS features appeared some time after the diagnosis of cancer.
- Seventy-six (71%) patients had thrombotic manifestations.
- Seventy-three (21%) fulfilled the Sapporo criteria.
- The main APS features included thrombocytopenia in 27 (25%) patients, stroke in 25 (24%), DVT in 20 (19%), and PE in 16 (15%) patients.
- LA was present in 70/104 (67%) patients, aCL in 70/104 (67%) (54 IgG aCL and 20 IgM aCL), anti-β2GPI in 6 (6%), and hemolytic anemia in 4 (4%) patients.
- Seventy-one (63%) out of 113 patients recovered or are still alive after cancer treatment.
- Clinically, pulmonary infarctions, kidney and adrenal involvement, intestinal thrombosis and splenic thrombosis were associated with a poor prognosis.
- Although information on the disappearance of aPL after cancer therapy was not available in all cases, 23 (35%) of 65 patients achieved aPL remission after treatment, especially those patients with lymphoma of the spleen and those who underwent nephrectomy.

8.3 CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME DURING PREGNANCY AND PUERPERIUM: MATERNAL AND FETAL CHARACTERISTICS OF 15 CASES.

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EXTENDED REPORT

Catastrophic antiphospholipid syndrome during pregnancy and puerperium: maternal and fetal characteristics of 15 cases

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Background: The catastrophic variant of the antiphospholipid syndrome (APS) is a life-threatening form of presentation of this syndrome that can be triggered by several factors.
Aim: To describe the characteristics of patients who developed catastrophic APS triggered during pregnancy and puerperium.
Methods: A review of the first 255 cases collected in the website-based ''CAPS Registry'' was undertaken. Three new and unpublished cases of catastrophic APS developed during pregnancy and puerperium were added.
Results: Fifteen cases were identified. The mean (range) age was 27 (17–38) years. Most patients had a previous unsuccessful obstetric history. In 7 of 14 (50%) cases with available medical history, the catastrophic APS appeared during pregnancy, in 6 (43%) during the puerperium and in 1 (7%) after curettage for a fetal death. The main clinical and serological characteristics were similar to those patients with catastrophic APS triggered by other factors, except for a history of a higher prevalence of previous abortions ($p<0.01$). Several specific features were found, including the HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome in 8 (53%) patients, placental infarctions in 4 (27%) patients, and pelvic vein thrombosis and myometrium thrombotic microangiopathy in 1 (7%) patient each. Mortality rate was high for the mothers (46%), and for the babies (54%).
Conclusions: It is important to consider the possibility of the development of catastrophic APS in those patients with signs of HELLP syndrome and multiorgan failure during pregnancy or puerperium, especially in those patients with previous history of abortions and/or thrombosis.

The antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterised by a combination of arterial and/or venous thrombosis, pregnancy morbidity, usually accompanied by a mild-to-moderate thrombocytopenia, and raised titres of antiphospholipid antibodies (aPL)—namely, the lupus anticoagulant (LA) and/or anticardiolipin antibodies (aCL).[1]

The most characteristic feature of obstetrical APS is miscarriage. Currently, recurrent miscarriage is a potentially treatable condition when it is associated with aPL.[2] Additionally, several other serious obstetric complications have been associated with APS, including pre-eclampsia, fetal growth restriction, uteroplacental insufficiency, fetal distress and medically induced preterm delivery.[3 4]

Catastrophic APS (also known as ''Asherson's syndrome'') is an unusual (<1%) but usually a life-threatening variant of APS, characterised by rapid appearance of multiple thromboses (mainly small-vessel thrombosis) that lead to multiorgan failure.[5] Since its first description in 1992,[5] several large series have been published,[6 7] and more than 250 patients have been collected in the international registry of patients with catastrophic APS (Catastrophic Antiphospholipid Syndrome (CAPS) Registry. Catastrophic events may be triggered, in >50% of patients, by a recognised factor, mainly infections, trauma or surgery, anticoagulation withdrawal, malignancies and lupus ''flares'', or appear infrequently during pregnancy (ie, after a caesarean section or fetal loss).

No previous publications have focused on the setting of catastrophic APS during the obstetric period. Our objective in this study was to assess the clinical and laboratory characteristics of the catastrophic APS triggered or presented during pregnancy and puerperium obstetric periods by analysing three new and unpublished cases in addition to 12 already published cases collected from the ''CAPS Registry'', with special interest in maternal and fetal outcome.

METHODS

We reviewed the 255 cases that were included in the website-based CAPS Registry on 1 November 2005. This registry was created by the European Forum on Antiphospholipid Antibodies, a study group devoted to the development of multicentre projects with large populations of patients with catastrophic APS. The website contains clinical, laboratory and

Abbreviations: aCL, anticardiolipin antibodies; aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; CAPS Registry, Catastrophic Antiphospholipid Syndrome Registry; CNS, central nervous system; DIC, disseminated intravascular coagulation; HELLP, haemolysis, elevated liver enzymes, low platelets; LA, lupus anticoagulant; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura

therapeutic data on all reported cases of patients with catastrophic APS and can be freely accessed through the internet (http://www.med.ub.es/MIMMUN/FORUM/CAPS.HTM). The sources of information are the personal communications of the physician who treated these patients and the periodically computer-assisted search (Medline, National Library of Medicine, Bethesda, Maryland, USA) of published reports to locate all cases of patients with catastrophic APS. Patients included in the CAPS Registry fulfil the classification criteria for catastrophic APS[8] (box 1). Cases were summarised using a standardised data form, including age, diagnosis of the underlying condition, time of presentation of catastrophic APS features (during pregnancy or puerperium periods), clinical manifestations, serological features, treatment and outcome.

We selected those patients who developed the catastrophic APS during pregnancy and puerperium. The list of precipitating factors in the CAPS registry was used as a guide for case identification; however, only those cases with a close relationship between pregnancy and/or puerperium and the development of the catastrophic APS event were included. Three previously unpublished cases with catastrophic APS occurring during pregnancy or puerperium were added to the review and subsequently included into the registry. The diagnosis of HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome was established if patients fulfilled the laboratory criteria proposed by Sibai *et al*,[9] including: (1) platelet count <100 000/mm^3, (2) aspartate aminotransferase >70 IU/l and (3) lactate dehydrogenase >600 U/l. Severity of HELLP syndrome was classified according to Martin *et al*'s[10] criteria based on platelet count. Class 1 (severe) was considered when platelet count was $<50\times10^9$/mm^3, class 2 (moderate) when platelet count was between 51×10^9 and 100×10^9/mm^3 and class 3 (mild) when platelet count was $>100\times10^9$/mm^3.

In order to identify whether patients with catastrophic APS triggered during pregnancy or puerperium correspond to a special subset of patients with catastrophic APS, we compared them with the rest of patients (n = 240) included in the CAPS Registry (χ^2 test, SPSS V.11.0).

Box 1: Preliminary criteria for the classification of catastrophic antiphospholipid syndrome

- Evidence of involvement of three or more organs, systems and/or tissues. Usually, clinical evidence of vessel occlusions, confirmed by imaging techniques when appropriate. Renal involvement is defined by a 50% rise in serum creatinine, severe systemic hypertension (>180/100 mm Hg) and/or proteinuria (> 500 mg/24 h).
- Development of manifestations simultaneously or in <1 week
- Confirmation of small-vessel occlusion in at least one organ or tissue by histopathology. For histopathological confirmation, significant evidence of thrombosis must be present, although vasculitis may coexist occasionally.
- Laboratory confirmation of the presence of antiphospholipid antibodies (aPL): lupus anticoagulant and/or anticardiolipin antibodies. If the patient was not previously diagnosed as with an antiphospholipid syndrome (APS), the laboratory confirmation requires that aPL is detected on two or more occasions at least 6 weeks apart (not necessarily at the time of the event), according to the proposed preliminary criteria for the classification of definite APS.

Definite catastrophic APS

- All four criteria

Probable catastrophic APS

- All four criteria, except for only two organs, systems and/or tissues involvement
- All four criteria, except for the absence of laboratory confirmation at least 6 weeks apart due to the early death of a patient never tested for aPL before the catastrophic APS

- Criteria 1, 2 and 4
- Criteria 1, 3 and 4, and the development of a third event in >1 week but in <1 month, despite anticoagulation

RESULTS

We analysed 15 cases of catastrophic APS that appeared during pregnancy or puerperium. (3 previously unpublished cases and 12 from the CAPS Registry[5 11–19]). Tables 1 and 2 summarise the data from these cases.

General characteristics and obstetric history

In all, 7 (47%) patients had primary APS, 7 (47%) had SLE and 1 (6%) had lupus-like syndrome. The mean (SD, range) age at the time of the catastrophic APS event was 27 (6 (17–38)) years. Past obstetric history was available in 14 cases. Only 1 patient had a previous successful pregnancy, 9 patients had previous abortions or fetal losses, and in 4 cases[11 13 16 19] there were no previous pregnancies. In 7 of the 14 (50%) cases catastrophic APS appeared during pregnancy (ranging from the 17th to 38th weeks of gestation), in 6 (43%) cases it presented during puerperium (ranging from the 2nd day until 3 weeks after delivery) and in 1 (7%) case it presented, 2 days after dilatation and curettage for a fetal death at 18 weeks of pregnancy. In 4 (26%) cases the catastrophic APS event was the first manifestation of the APS (cases 1, 6, 11 and 13). Only 6 (40%) patients fulfilled the diagnostic criteria for APS prior to the catastrophic APS event. The remaining patients had some features suggestive of APS or previous aPL-positive determinations. At the moment of the catastrophic APS event, only 2 patients (cases 2 and 10) were under treatment (aspirin 325 mg/day and warfarin, respectively).

Thrombotic and APS-related features

The main clinical symptoms were renal involvement in 11 (73%) patients (in 3 of them in the form of renal thrombotic microangiopathy (TMA)) pulmonary involvement in 11 (73%) patients (acute respiratory distress syndrome (ARDS) in four patients, respiratory failure in three, pulmonary embolism in two, and alveolar hemorrhage, pulmonary infarcts and pulmonary TMA in one case each), central nervous system (CNS) involvement in 9 (60%) patients (cerebral infarcts in five cases, encephalopathy in two cases, cerebral haemorrhage in two cases, transient ischaemic attack in one case, cerebral TMA in one case and status epilepticus in one case) and HELLP syndrome in 8 (53%) patients. Seven patients had a class 1 HELLP syndrome, whereas only 1 patient had class 2. The mean platelet count among patients with HELLP syndrome was 29 000/mm^3 (ranging from 6000 to 59 000).

Intra-abdominal and pelvic features included placental infarctions in 4 (27%) patients, gastrointestinal thrombosis in 4 (27%; including mesenteric and intestinal thrombosis), hepatic thrombosis in 3 (20%), adrenal involvement in 2 (13%; haemorrhage in one case and adrenal infarcts in another), portal vein thrombosis in 1 (7%), inferior vena cava

Table 1 General characteristics of patients with catastrophic antiphospholipid syndrome during pregnancy or puerperium

	Age (year)	Diagnosis	Previous obstetric history	Time of onset
Bendon *et al*[11]	22	SLE	No previous pregnancies	30 weeks of gestation
Hochfeld *et al*[12]	37	PAPS	Three previous spontaneous abortions	2nd day after fetal death
Kupferminc *et al*[13]	17	PAPS	No previous pregnancies	5th day of puerperium
Kitchens[14]	38	SLE	NR	38 weeks of gestation
Wislowska[15]	26	SLE	One previous successful pregnancy	25 weeks of gestation
Sinha *et al*[16]	22	SLE	No previous pregnancies	25 weeks of gestation
Asherson *et al*[5]	22	SLE	One spontaneous abortion	20 wks of gestation
Asherson *et al*[5]	27	PAPS	One fetal loss	Post-fetal loss
Ortiz *et al*[17]	32	Lupus-like	One second trimester fetal loss	2nd day of puerperium
Koenig *et al*[18]	19	PAPS	One miscarriage	17 weeks of gestation
Coward *et al*[19]	30	PAPS	No previous pregnancies	3rd weeks of puerperium
Wieser M *et al**	33	PAPS	One first trimester spontaneous abortion	5th day of puerperium
Present case 1	29	SLE	Eight previous spontaneous abortions	28 weeks of gestation
Present case 2	26	SLE	Two previous fetal losses	3rd day of puerperium
Present case 3	28	PAPS	One second trimester fetal loss	6th day of puerperium

NR, not reported; PAPS, primary antiphospholipid syndrome; Ref, reference; SLE, systemic lupus erythematosus.
*Included previously in the ''CAPS Registry''.

thrombosis in 1 (7%), splenic infarcts in 1 (7%), pelvic vein thrombosis in 1 (7%) and myometrium TMA in 1 (7%).

Other manifestations were skin involvement in 5 (33%) patients (livedo reticularis in two cases, and skin ulcers, skin thrombosis and digital necrosis in one case), heart involvement in 3 (20%) patients in the form of myocardial infarction, valve disease and myocardial TMA in one case each, deep vein thrombosis in 3 (20%) patients, bone marrow involvement in 2 (13%) patients (bone marrow necrosis in one and bone marrow hypoplasia in the other) and bone necrosis in 1 (7%) patient.

Laboratory features

Severe thrombocytopenia was found in 2 (13%) patients without HELLP syndrome, schistocytes were found in 3 (20%) patients, disseminated intravascular coagulation (DIC) features in 3 (20%), haemolytic anaemia in 2 (13%) and severe pancytopenia in 2 (13%). In all, 14 (93%) patients were positive for aCL, 12 (80%) for the IgG isotype and 4 (27%) for the IgM isotype. LA was found in 10 (73%) patients, and anti-β2 glycoprotein I (GPI) antibodies in 3 (20%).

Treatment and maternal and fetal outcomes

A total of 6 (40%) patients (cases 2, 6, 9, 10, 11 and 13) were under anticoagulation treatment (low molecular weight heparin) before a catastrophic APS event. Specific treatment for the catastrophic APS events was available in 14 cases. In all, 11 (79%) out of 14 patients received anticoagulation, 10 (71%) steroids, 4 (29%) plasma exchange, 3 (21%) dialysis, 3 (21%) cyclophosphamide, 3 (21%) intravenous immunoglobulins, 2 (14%) fresh frozen plasma and 1 (7%) fibrinolysis.

In all, 7 (46%) mothers died due to the catastrophic APS. Fetal outcome was available in 13 cases. Only 6 (46%) babies survived (3 of them were premature newborns), whereas 7 (54%) babies died. Neither the mothers nor the babies had different outcomes regarding the previous presence of HELLP syndrome or the treatment received (non-statistically significant differences), including the combined therapies (anticoagulation and plasma exchange). Regarding the babies who survived, in 2 cases their mothers had received plasma exchange. However, in 2 of the babies who died, their mothers had also received plasma exchange therapy.

Comparison between patients with pregnancy or puerperium-associated catastrophic APS

Fifteen patients with catastrophic APS events associated with pregnancy or puerperium were compared with 240 patients with catastrophic APS events not associated with pregnancy or puerperium that were included in the CAPS Registry (table 3). In the former group, there was a higher prevalence of previous abortions ($p<0.001$). In those patients with catastrophic APS events not related to pregnancy or puerperium, there was a higher prevalence of cardiac involvement ($p = 0.02$) and livedo reticularis ($p = 0.025$), and they had a higher prevalence of catastrophic events as the initial manifestation of APS ($p = 0.05$).

DISCUSSION

Pregnancy is a well-recognised hypercoagulable state that encompasses a period of 10–11 months (including puerperium). This hypercoagulability is explained by many factors, including alterations in coagulation proteins (increased levels of factors II, V, VII, VIII, X and XII as well as von Willebrand factor, and decreased levels of protein S and activated protein C) and alterations in fibrinolytic systems (low plasma fibrinolytic activity during pregnancy, labour and delivery), with a decreased activity of tissue plasminogen activator.[20 21] The presence of microparticles derived from maternal endothelial cells, platelets and placental trophoblasts may also contribute to the procoagulant situation.[20] Additionally, the reduction of venous flow in lower extremities as a result of compression by the gravid uterus and the prolonged bed rest (especially during labour and postpartum) induces venous stasis and contributes to the formation of thrombosis. The risk of venous thrombosis is 5–6-fold higher during pregnancy compared with non-pregnant women of similar age.[21] Despite this situation, deep venous thrombosis is not commonly reported during pregnancy, occurring in 1 in 1000 to 1 in 2000 pregnancies;[21] however, this prevalence may be higher in the presence of any thrombophilic factor.

Thrombophilic disorders notably increase gestational vascular complications, leading to pre-eclampsia, retardation of fetal growth, placental abruption, placental thrombosis and recurrent miscarriages. Several thrombophilic disorders have been described during pregnancy, including antithrombin deficiency, protein S and protein C deficiency, factor V Leiden and prothrombin gene mutation, hyperhomocysteinaemia and aPL, among others.[22] Routine assessment of these factors is not currently recommended in healthy pregnant women. It is only indicated in those women with previous thrombosis and/or recurrent pregnancy losses.[22]

HELLP syndrome is a manifestation of pre-eclampsia occurring in approximately 0.6% of all pregnancies.[23] It involves smaller terminal arterioles and is a process with characteristic histological features. The microangiopathic haemolytic anaemia and the raised liver enzymes are explained by platelet-fibrin

Table 2 Clinical and serological characteristics and outcome of patients with catastrophic antiphospholipid syndrome during pregnancy or puerperium

Author (CAPS registry number)	Catastrophic APS features	Laboratory findings	Treatment	Outcome	
				Maternal	Fetal
Bendon *et al*[11]*(6)	Placental infarctions myocardium, renal, gastrointestinal and myometrium TMA	Severe thrombocytopenia Schistocytes aCL positive LA: ND	NR	Death	Intrauterine fetal death
Hochfeld *et al*[12] (22)	HELLP, iliac, pelvic vein and skin thrombosis Renal failure, cerebral, cardiac Pulmonary, splenic and adrenal Infarcts, cerebral haemorrhage	DIC LA positive IgG aCL (high titres)	Anticoagulation (IV heparin) Steroids Cyclo Plasma exchange	Death	Intrauterine fetal death
Kupferminc *et al*[13]†(31)	HELLP, ARDS Placental infarcts, renal failure Alveolar haemorrhage	LA positive IgG aCL (26.5 GPL)	Steroids Plasma exchange Dialysis	Recovery	Prematurity
Kitchens[14]*(65)	HELLP, portal vein Inferior cava, hepatic and mesenteric vein thrombosis	aCL strongly positive LA negative	Anticoagulation (IV hepatin) Streptokinase	Recovery	NR
Wislowska *et al*[15]* (82)	ARDS, encephalopathy Rapid progressive nephritis Skin ulcers	LA positive IgG aCL moderate levels	Anticoagulation (LMWH) Steroids Cyclo	Recovery	Miscarriage
Sinha *et al*[16]* (100)	HELLP Placental infarcts Cerebral infarcts Bone marrow necrosis	Severe pancytopenia IgG aCL (203 GPL) IgM aCL (10 MPL) LA positive, B2GP1 IgG	Steroids Plasma exchange IVIG	Death	Death (intracerebral haemorrhage)
Asherson *et al*[7]*(110)	HELLP Renal TMA, ARDS Cerebral infarcts	Thrombocytopenia Schistocytes, LA positive IgG and IgM aCL positive	Steroids Cyclo Anticoagulation (IV heparin)	Recovery	Death
Asherson *et al*[7] (121)	PE, digital necrosis Hepatic, renal, intestinal and mesenteric thrombosis	Haemolytic anaemia IgG aCL (72 GPL) LA negative	Steroids Anticoagulation	Death	Death
Ortiz *et al*[17]† (240)	Renal TMA, valve lesions Multiple cerebral infarcts	Thrombocytopenia Haemolytic anaemia Schistocytes, LA positive IgG aCL (>120 GPL) IgM aCL (19.2 MPL)	Steroids, FFP Anticoagulation (LMWH)	Recovery	NR
Koenig *et al*[18]*(251)	HELLP Hepatic infarctions Bone necrosis, bowel TMA	Severe thrombocytopenia IgG and IgM aCL positive B2GP1, LA positive	Anticoagulation (LMWH) FFP	Recovery	Death
Coward *et al*[19]†(252)	TIA, status epilepticus Renal failure, brain and pulmonary TMA Adrenal haemorrhage	LA positive	Anticonvulsants Dyalysis	Death	Healthy child
Weiser M(‡)†(99)	HELLP, ARDS Renal failure, cerebral infarctions and haemorrhage	Severe thrombocytopenia IgG aCL (>100 GPL) LA positive	Steroids, IVIG Anticoagulation Dyalysis	Death	Healthy child
Present case 1*	HELLP, bone marrow hypoplasia, renal failure DVT, respiratory failure Livedo reticularis	DIC Pancytopenia IgG aCL high titres LA negative	Steroids Anticoagulation (LMWH)	Death	Prematurity
Present case 2†	DVT, PE TIA, respiratory failure	IgG aCL high titres LA negative	Anticoagulation (LMWH) Steroids, IVIG	Recovery	Healthy child
Present case 3†	Placental infarctions Renal failure, encephalopathy Respiratory failure	Severe thrombocytopenia LA positive, DIC, aCL IgG (24 U/ml) B2GP1 IgG (44.9 U/ml)	Anticoagulation (LMWH) Plasma exchange	Recovery	Healthy child

aCL, anticardiolipin antibodies; APS, antiphospholipid syndrome; ARDS, acute respiratory distress syndrome, B2GP1, β2-glycoprotein 1 antibodies; Cyclo, cyclophosphamide; DIC, disseminated intravascular coagulation; DVT, deep vein thrombosis; FFP, fresh frozen plasma; HELLP, haemolysis, elevated liver enzymes, low platelet count; IVIG, intravenous immunoglobulins; LA, lupus anticoagulant; LMWH, low molecular weight heparin; ND, not done; NR, not reported; PE, pulmonary embolism; TIA, transient ischaemic attack; TMA, thrombotic microangiopathy.
*Presenting during pregnancy.
†Presenting during puerperium.
‡This case was included in the CAPS registry by Manfred Weiser, Salzburg, Austria.

deposits and thrombi causing fragmentation of red cells as they pass through interrupted arterioles and hepatic sinusoid blood flow restrictions, respectively. Thrombocytopenia is due to the increased consumption of platelets after their adhesion to damaged endothelium and intravascular aggregation.[24]

The real incidence of HELLP syndrome in APS is difficult to estimate. Around 50 well-documented cases are reported with both conditions. Von Tempelhoff *et al*[25] studied several thrombophilic factors, including LA and aCL, in a series of 32 patients with HELLP syndrome. Of these, 17 (53%) patients were positive for LA and 15 (47%) were positive for aCL. Thuong *et al*[26] described 16 episodes of HELLP in 15 patients with APS. In 8 of these cases, HELLP syndrome revealed an APS (patients with previously unknown APS). In all, 11 (69%) and 3 (19%) patients had pre-eclampsia and eclampsia, respectively. In a significant proportion of cases (44%) HELLP syndrome occurred during the second trimester, and in 12% during 18–20 weeks of gestation. The authors concluded that HELLP appears in a more severe form in early stages of pregnancy in patients with APS than in the general population.

In the present study, we found eight patients with HELLP syndrome; most of them were classifiable as class 1 (severe)

Table 3 Comparison between patients with catastrophic antiphospholipid syndrome related and those not related to pregnancy or puerperium

	Catastrophic APS related to pregnancy and puerperium n = 15 (%)	Catastrophic APS not related to pregnancy or puerperium n = 240 (%)	p Value
Feature			
Catastrophic APS as a first manifestation	3 (20)	114 (47)	0.05
Previous APS features	10 (67)	127 (53)	NS
Previous abortions	9 (60)	41 (17)	<0.001
DVT	3 (20)	76 (32)	NS
Peripheral arterial thrombosis	0 (0)	27 (11)	NS
Cardiac involvement	3 (20)	128 (33)	0.02
Valvular disease	1 (7)	49 (20)	NS
Pulmonary involvement	11 (73)	159 (66)	NS
ARDS	5 (33)	60 (25)	NS
Renal involvement	10 (67)	175 (73)	NS
Cerebral involvement	9 (60)	151 (63)	NS
Cutaneous involvement	5 (33)	124 (52)	NS
Livedo reticularis	2 (13)	66 (27)	0.025
Death	7 (47)	111 (46)	NS

ARDS, acute respiratory distress syndrome; DVT, deep venous thrombosis; NS, not significant.

HELLP syndrome. This is, however, not a very helpful classification tool in this particular group of patients (SLE, aPL, related septic process, etc). Nonetheless, severe HELLP syndrome seems to be a major feature of catastrophic APS during the obstetric period. This is supported by data observed in six of eight collected cases with HELLP syndrome. In the case described by Hochfeld *et al*,[12] HELLP syndrome was characterised by a persistent thrombocytopenia. In the case described by Kupferminc *et al*,[13] HELLP syndrome improved only after plasma exchange sessions. Portal and hepatic vein thrombosis and an inferior vena cava thrombosis accompanied the HELLP syndrome in the patient documented by Kitchens *et al*.[14] In the case described by Koenig *et al*,[18] the patient had abdominal pain, requiring a laparotomy, which did not reveal any abnormality. Only a CT scan revealed concomitant hepatic infarctions. Interestingly, in the case described by Sinha *et al*,[16] the HELLP syndrome deteriorated despite the termination of pregnancy. Finally, in our first case, HELLP had an unsatisfactory course in relation to surgical wound infection and haematoma formation.

As these microangiopathic disorders share several clinical and serological characteristics, the differential diagnosis in pregnant patients may be difficult, but necessary, because it carries different therapeutic strategies—eg, plasma exchange sessions for those cases with thrombotic thrombocytopenic purpura (TTP) and prompt delivery for those cases of HELLP syndrome. There are several clinical features that may differentiate each disorder. In TTP, the involvement of the CNS is higher than in HELLP syndrome, which involves mainly liver parenchyma. TTP induces a more severe thrombocytopenia and haemolytic anemia than HELLP syndrome. Anti-thrombin and D-dimers are normal in TTP, whereas they are abnormal in patients with HELLP syndrome. In some severe HELLP syndrome and pre-eclampsia cases, diverse organs may be affected, leading to acute renal failure, myocardial dysfunction, DIC, ascites, pulmonary oedema, cerebral oedema, subcapsular liver haematoma and ARDS, among others.[26] There are additional diagnostic challenges for clinicians. Patients with catastrophic APS develop a wide spectrum of clinical and haematological features including CNS involvement, HELLP syndrome, DIC[27] and microangiopathic thrombosis. In patients with catastrophic APS, combined treatments are needed, including, in many cases, plasma exchange sessions, as well as termination of pregnancy in those cases with related pre-eclampsia or eclampsia.

Catastrophic APS during pregnancy or puerperium represents almost 6% of all cases (15/255) described with catastrophic APS. This represents a life-threatening situation with a high mortality rate in these young women of childbearing age. This also represents a unique scenario where many factors may participate as additional potential trigger factors, including infections such as endometritis, caesarean wound or episiotomy wound infection or mastitis, lupus flares, anticoagulation withdrawal during the actual labour, among others.

The relatively small number of patients with catastrophic APS during the obstetric period makes it difficult to definitely conclude whether this group corresponds to or singles out a different subset of patients with catastrophic APS. However, these patients seem to have a higher prevalence of previous abortions than the non-pregnant patients with catastrophic APS.

On the basis of present data and as per previous guidelines for the treatment of catastrophic APS,[8] we propose the following scheme for the management of catastrophic APS during pregnancy (management of catastrophic APS during puerperium could be similar to that in other scenarios). First, it is essential to prevent any potential trigger factor, mainly infections, and to maintain an adequate anticoagulation in those patients with previous thromboses and aPL. The second aspect is to evaluate fetus maturation. When pulmonary fetal maturation is ready, a prompt delivery is recommended. In those cases with HELLP or other microangiopathic features, plasma exchange sessions are certainly strongly indicated. Plasma exchange sessions have been used previously in mothers with other life-threatening conditions.[28 29] The remaining therapeutic measures recommended in catastrophic APS are also useful, specially steroids and intravenous immunoglobulins. It is important to bear in mind that pre-term delivery is the strongest risk factor for an adverse neonatal outcome, but it can be life saving for the mother and the fetus.

In conclusion, it is important to consider the possibility of the development of catastrophic APS in those patients with signs of TMA (with or without HELLP syndrome) and/or multiorgan failure during pregnancy or puerperium, particularly in those patients with a history of abortions and/or thrombosis.

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REFERENCES

1 **Cervera R**, Piette JC, Font J, Khamashta MA, Shoenfeld Y, Camps MT, *et al.* Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1000 patients. *Arthritis Rheum* 2002;**46**:1019–27.
2 **Cervera R**, Balasch J. The management of pregnant patients with antiphospholipid syndrome. *Lupus* 2004;**13**:683–7.
3 **Branch DW**, Khamashta MA. Antiphospholipid syndrome: obstetric diagnosis, management, and controversies. *Obstet Gynecol* 2003;**101**:1333–44.
4 **Carmona F**, Balasch J. Fetal and obstetric manifestations and infertility in the antiphospholipid syndrome. In: Asherson RA, Cervera R, Piette, Shoenfeld Y, eds. *The antiphospholipide syndrome II:autoimmune thrombosis*. Amsterdam: Elsevier, 2000:205–11.
5 **Asherson RA**. The catastrophic antiphospholipid syndrome. *J Rheumatol* 1992;**19**:508–12.
6 **Asherson RA**, Cervera R, Piette JC, Font J, Lie JT, Burcoglu A, *et al.* Catastrophic antiphospholipid syndrome. Clinical and laboratory features of 50 patients. *Medicine (Baltimore)* 1998;**77**:195–207.
7 **Asherson RA**, Cervera R, Piette JC, Shoenfeld Y, Espinosa G, Petri MA, *et al.* Catastrophic antiphospholipid syndrome: clues to the pathogenesis from a series of 80 patients. *Medicine (Baltimore)* 2001;**80**:355–77.
8 **Asherson RA**, Cervera R, de Groot PG, Erkan D, Boffa MC, Piette JC, *et al.* Catastrophic Antiphospholipid Syndrome Registry Project Group. Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines, *Lupus* 2003;**12**:530–4.
9 **Sibai BM**, Taslimi MM, el-Nazer A, Amon E, Mabie BC, Ryan GM. Maternal-perinatal outcome associated with the syndrome of hemolysis, elevated liver enzymes, and low platelets in severe preeclampsia-eclampsia. *Am J Obstet Gynecol* 1986;**155**:501–9.
10 **Martin JN Jr**, Rinehart BK, May WL, Magann EF, Terrone DA, Blake PG. The spectrum of severe preeclampsia: comparative analysis by HELLP (hemolysis, elevated liver enzyme levels, and low platelet count) syndrome classification. *Am J Obstet Gynecol* 1999;**180**:1373–84.
11 **Bendon RW**, Wilson J, Getahun B, van der Bel-Kahn J. A maternal death due to thrombotic disease associated with anticardiolipin antibody. *Arch Pathol Lab Med* 1987;**111**:370–2.
12 **Hochfeld M**, Druzin ML, Maia D, Wright J, Lambert RE, McGuire J. Pregnancy complicated by primary antiphospholipid antibody syndrome. *Obstet Gynecol* 1994;**83**:804–5.
13 **Kupferminc MJ**, Lee MJ, Green D, Peaceman AM. Severe postpartum pulmonary, cardiac, and renal syndrome associated with antiphospholipid antibodies. *Obstet Gynecol* 1994;**83**:806–17.
14 **Kitchens CS**. Thrombotic storm: when thrombosis begets thrombosis. *Am J Med* 1998;**104**:381–5.
15 **Wislowska M**. Successful treatment of catastrophic antiphospholipid syndrome in a pregnant woman. *Clin Exp Rheumatol* 1999;**17**:261.
16 **Sinha J**, Chowdhry I, Sedan S, Barland P. Bone marrow necrosis and refractory HELLP syndrome in a patient with catastrophic antiphospholipid antibody syndrome. *J Rheumatol* 2002;**29**:195–7.
17 **Ortiz P**, Castro A, Valles M, Coll E, Casas M, Mauri JM. Catastrophic antiphospholipid syndrome in the immediate puerperium. *Nefrologia* 2003;**23**:459–62.
18 **Koenig M**, Roy M, Baccot S, Cuilleron M, de Filippis JP, Cathebras P. Thrombotic microangiopathy with liver, gut, and bone infarction (catastrophic antiphospholipid syndrome) associated with HELLP syndrome. *Clin Rheumatol* 2005;**24**:166–8.
19 **Coward LJ**, Kullmann DM, Hirsch NP, Howard RS, Lucas SB. Catastrophic primary antiphospholipid syndrome presenting as status epilepticus. *J Neurol Neurosurg Psychiatry* 2005;**76**:1607–8.
20 **Brenner B**. Haemostatic changes in pregnancy. *Thromb Res* 2004;**114**:409–14.
21 **Toglia MR**, Weg JG. Venous thromboembolism during pregnancy. *N Engl J Med* 1996;**335**:108–14.
22 **Kujovich JL**. Thrombophilia and pregnancy complications. *Am J Obstet Gynecol* 2004;**191**:412–24.
23 **Egerman RS**, Sibai BM. HELLP syndrome. *Clin Obstet Gynecol* 1999;**42**:381–9.
24 **O'Brien JM**, Barton JR. Controversies with the diagnosis and management of HELLP syndrome. *Clin Obstet Gynecol* 2005;**48**:460–77.
25 **von Tempelhoff GF**, Heilmann L, Spanuth E, Kunzmann E, Hommel G. Incidence of the factor V Leiden-mutation, coagulation inhibitor deficiency, and elevated antiphospholipid-antibodies in patients with preeclampsia or HELLP syndrome. Hemolysis, elevated liver-enzymes, low platelets. *Thromb Res* 2000;**100**: 363–5.
26 **Le Thi Thuong D**, Tieulié N, Costedoat N, Andreu MR, Wechsler B, Vauthier-Brouzes D, *et al.* The HELLP syndrome in the antiphospholipid syndrome: retrospective study of 16 cases in 15 women. *Ann Rheum Dis* 2005;**64**:273–8.
27 **Asherson RA**, Espinosa G, Cervera R, Gómez-Puerta JA, Musuruana J, Bucciarelli S, *et al.* Disseminated intravascular coagulation in catastrophic antiphospholipid syndrome: clinical and haematological characteristics of 23 patients. *Ann Rheum Dis* 2005;**64**:943–6.
28 **Hayward CPM**, Sutton DMC, Carter WH, Campbell ED, Scott JG, Francombe WH, *et al.* Treatment outcomes in patients with adult thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. *Arch Intern Med* 1994;**154**:982–7.
29 **Shamseddine A**, Chehal A, Usta I, Salem Z, El-Saghir N, Taher A. Thrombotic thrombocytopenic purpura and pregnancy: report of four cases and literature review. *J Clin Apheresis* 2004;**19**:5–10.

APPENDIX

THE CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME REGISTRY PROJECT GROUP (EUROPEAN FORUM ON ANTIPHOSPHOLIPID ANTIBODIES)

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8.3 Summary of results

We analyzed 15 cases of CAPS that appeared during pregnancy or the puerperium (3 previously unpublished cases and 12 from the CAPS Registry).

- Mean age at the time of the CAPS event was 27 years (range, 17–38 yrs).
- Past obstetric history was available in 14 cases. Only 1 patient had a previous successful pregnancy, 9 patients had previous abortions or fetal losses, and in 4 cases there were no previous pregnancies.
- In 7 of the 14 (50%) cases, CAPS appeared during pregnancy (ranging from the 17^{th} to 38^{th} week of gestation), in 6 (43%) cases it presented during puerperium (ranging from the 2nd day until 3 weeks after delivery) and in 1 (7%) after curettage for a fetal death.
- In 4 (26%) cases the CAPS event was the first manifestation of APS.
- The main clinical and serological characteristics were similar to those of patients with CAPS triggered by other factors, except for a higher prevalence of previous abortions.
- The main clinical symptoms were renal involvement in 11 (73%) patients, pulmonary involvement in 11 (73%), CNS involvement in 9 (60%) and HELLP syndrome in 8 (53%) patients.
- Other specific features found in these patients included placental infarctions in 4 (27%) patients, pelvic vein thrombosis in 1 (7%) and myometrial TMA in 1 (7%) patient.
- Fourteen (93%) patients were positive for aCL, 12 (80%) for the IgG isotype and 4 (27%) for the IgM isotype. LA was found in 10 (73%) patients, and anti-β2GPI in 3 (20%) patients.
- Seven (46%) mothers died due to the CAPS. Fetal outcome was available in 13 cases. Only 6 (46%) babies survived (3 premature newborns), whereas 7 (54%) babies died. Neither the mothers nor the babies had different outcomes regarding the previous presence of HELLP

syndrome or the treatment received, including the combined therapies (anticoagulation and plasma exchange).

9. DISCUSSION

Interest in APS has grown rapidly in recent years, with an increasing number of patients being identified. Most clinicians now agree that primary APS is a distinct, recognizable disorder with arterial and venous thrombosis and pregnancy loss as the main clinical features. Although the early description by Hughes (134), almost 25 years ago, was in patients affected by SLE, primary APS is being recognized with increasing frequency. The ongoing Euro-Phospholipid Project found primary APS to be more frequent than associated APS (20).

Higher frequencies of some complications have been described in a higher frequency in patients with APS associated with SLE, including thrombocytopenia, autoimmune hemolytic anemia, neutropenia, low C4 levels, cardiac valvular lesions and chorea (19,135). Soltesz et al (21) also found a higher prevalence of cerebrovascular thrombosis in APS associated with SLE.

To the best of our knowledge, our series is one of the largest and with a longer follow-up series of primary APS patients. Table 5 shows the different published series of patients with primary APS, including their main clinical characteristics and the number of patients who evolve into SLE or LLD (17, 22, 136-141).

We found a high prevalence of neurologic events in our patients: 40% had migraine, 26% developed stroke, 23% presented TIA, 16% had seizures and 8% had cognitive dysfunction (mainly memory problems). In a series of 323 patients with SLE, Sanna et al (142) found an association between aPL and the development of cerebrovascular disease, headache and seizures. Additionally, LA was independently associated with white matter hyperintensity lesions on brain MRI.

Table 5. Series of patients with primary APS

Author(Year) [REF]	Population	No. Patients	Mean age (yrs)	Mean Follow-up (range)	Main APS features %		Mortality %	Evolve into SLE	Evolve into LLD
1. Asherson et al (1989) [17]	British	70	38	5 yr (NA)	DVT	54	NA	0	0
					Arterial thrombosis	44			
					Pregnancy loss	34			
2. Vianna et al (1994) [19]	*Multicenter* British, Spanish	58	32	2 yr (0-5)	Pregnancy loss	53	NA	0	0
					DVT	50			
					Arterial thrombosis	36			
2. Mujic et al (1995) [136]	British	80	31	6 yr (1-28)	DVT	49	NA	2	1
					Pregnancy loss	40			
					Arterial thrombosis	30			
3. Múñoz-Rodriguez et al (1999) [137]	Spanish	62	36	4 yr (0-12)	Pregnancy loss	60	NA	NA	NA
					Thrombocytopenia	52			
					Arterial thrombosis	32			
4. Erkan et al (2000) [138]	N. American	39	27	14 yr (10-22)	Pregnancy loss	77	NA	NA	NA
					Neurologic events	62			
					Thrombocytopenia	41			
5. Gattorno et al (2003) [22]	Italian	14	9	6 yr (2-16)	DVT	43	NA	2	0
					Stroke	36			
					Thrombocytopenia	21			
6. Girón-Gonzalez et al (2004) [139]	Spanish	133	44	3 yr (NA)	Pregnancy loss	51	6.7	NA	NA
					DVT	46			
					Arterial thrombosis	31			
7. Medina et al (2004) [140]	Mexican	29	29	4 yr (NA)	DVT	69	3.4	NA	NA
					Thrombocytopenia	31			
					Stroke	21			
8. Krause et al (2005) [141]	*Multicenter* Israeli, Yugoslavian Slovakian	173	40	7 yr (NA)	DVT	58	NA	NA	NA
					Arterial thrombosis	49			
					Pregnancy loss	32			
9. Gómez-Puerta et al (2005)	*Multicenter* British Spanish , Mexican	128	42	9 yr (2-15)	Pregnancy loss	55	12	11	6
					Arterial thrombosis	49			
					DVT	48			

NA: Not available, REF: Reference.

A high proportion of patients (33 of 53) who underwent cerebral MRI had small high-intensity lesions suggestive of vasculopathy, but only 10 (8%) patients developed some degree of cognitive impairment. Recently, Vermeer et at (143), in a selected non-aPL elderly population, demonstrated a close relationship between the presence of small silent infarcts and the subsequent appearance of dementia, cognitive function decline, and stroke.

Cognitive impairment is not unusual in patients with APS. Recently, Tektonidou et al (144), using neuropsychological tests and MRI, evaluated 61 patients with APS (39 with primary APS) and compared them with 60 healthy individuals matched for age, sex, and education. Twenty-five (42%) of the 60 patients had cognitive deficits compared with 11 (18%) healthy control subjects. The most commonly involved cognitive domains were complex attention and verbal fluency. No relationship was detected between cognitive dysfunction and prior CNS disease. The authors found a significant association between cognitive dysfunction and *livedo reticularis* and between cognitive dysfunction and the presence of white matter lesions in the brain MRI. In our recently published series of 30 patients with dementia associated with APS (63), 14 (47%) out of 30 had silent infarcts. Of 1000 patients with APS from the European cohort a prevalence of 2.5% was reported for multi-infarct dementia, but no data were provided on subtle forms of cognitive dysfunction.

Ten (8%) out of 128 patients from our cohort presented MS-like features. Cuadrado et al (145) described 27 patients with APS with neurologic symptoms that mimicked MS. These patients were assessed by MRI which was compared with the MRI of 25 definite MS patients who did not have aPL. Neurologic symptoms and the physical examination of APS patients did not differ from those of MS patients. Globally MS patients had significantly increased severity scores in the white matter cerebellum and pons. Taken individually, MRI from APS patients could not be distinguished from those of MS patients. Interestingly, in the majority

of APS MS-like patients who received anticoagulation, no further neurological events were recorded. Finally, the authors recommended routine testing for aPL in all patients with MS.

At baseline, 44% of our patients had cardiac abnormalities (mainly mitral and aortic valve disease) in the TTE. In 27 patients, a new heart ultrasound evaluation was performed. New echocardiographic findings were found in 6 (22%) patients. Two patients had mitral valve disease; 2, ischemic changes; 1, aortic valve disease; and 1 patient developed mitral and aortic valve disease.

A variety of cardiac valve lesions have been associated with aPL in primary APS and SLE. Echocardiographic studies have shown that SLE patients with aPL have a higher prevalence of valvular lesions (mainly mitral and aortic lesions) than those without aPL. The valvular lesions consist mainly of superficial or intravascular fibrin deposits and their subsequent organization: vascular proliferation, fibroblast influx, and rigidity, leading to functional abnormalities. These may represent a potential cardiac source of stroke. Espinola-Zavaleta et al (23) studied 25 patients with primary APS using TEE. The average time between the first and follow-up TEE was 83 months. In the first TEE, valve lesions were found in 17 (70%) patients, MI in 5 (29%), pulmonary hypertension in 4 (23%) and calcified thrombi in 1 patient. Five-year follow-up TEE was performed in 12 patients, finding 3 new valve lesions in 3 patients and valve lesions progression in 6 patients.

Another prospective Italian study included 56 patients with primary APS who underwent to TEE (146). The first TEE study showed cardiac involvement (thickening or vegetations) in 34 subjects (61%), with mitral valve thickening, the most common abnormality. Embolic sources were found in 14 patients, associated with mitral valve thickening or stenosis in 10 patients. Over the 5-year follow-up, cardiac involvement was unchanged in 30 subjects (64%). New cardiac abnormalities were observed in 17 patients (36%), 15 (88%) of whom had high titers of IgG isotype aCL.

One of the major features of APS in women is pregnancy loss, most typically in the second trimester. Some women suffer six or more miscarriages before the diagnosis is made. The combination of IgG aCL and LA with a history of repeated pregnancy losses is associated with only a 10 to 20% chance of a live birth without treatment. Recurrent pregnancy loss is a common health problem affecting 1–2% of women of reproductive age; APS is the main treatable cause of recurrent miscarriages. It seems that women with APS associated with SLE have poorer pregnancy outcomes than do women with primary APS. The past medical history of successful deliveries was lower in our cohort (45%) compared with that in other series (147-148); a possible reason for the difference is that our principal study center is a referral center for women with a history of 3 or more miscarriages or 1 or more fetal deaths in association with aPL.

We found 6 patients with hemolytic anemia accompanied by positive Coombs tests in 5 (4%) cases. After multivariate analysis, positivity of the Coombs test was related with the development of SLE in patients with primary APS. Rottem et al (149) analyzed the clinical significance of autoimmune hemolytic anemia (AIHA) in 308 patients with APS. AIHA was documented in 32 (10.4%) patients. The authors found a highly significant association between AIHA and cardiac valvular vegetations and thickening, arterial thrombosis, *livedo reticularis* and CNS involvement (epilepsy or chorea).

The mortality rate in the current study was slightly higher (12%) than in similar studies (8–10%) with long-term follow-up of patients with aPL (121, 134). One possible explanation for the high mortality rate is the fact that all patients who died came from a cardiovascular referral center participating in the study. Information about the long term prognosis in primary APS is limited. Reshetniak et al (150) retrospectively studied 248 patients admitted to a Russian rheumatology unit for 8 years. Primary APS was diagnosed in 35 patients, APS associated with SLE in 122 patients and SLE without APS in 91 patients.

The 8-year survival was 98% for SLE patients without APS, 75% for those with SLE + APS and 83% for patients with primary APS. The presence of APS in SLE patients was significantly associated with high mortality. Ruiz-Irastorza et al (151) evaluated the impact of APS in a cohort of 202 SLE patients over a mean period of 10 years. Twenty-eight out of 202 patients fulfilled the Sapporo citeria for APS. The authors found a greater irreversible organ damage (measured by SLE damage index) in patients with APS. Cumulative survival at 15 years was lower in those patients with APS than in those without APS (65% vs 90%; p=0.03). Additionally, APS was an independent predictor factor of mortality.

Shan et al (152) reported the 10-year follow-up of 52 patients with raised levels of aCL. These included 31 patients with APS, of whom 10 had primary APS. Vascular events and pregnancy loss were found in 40% of the patients with primary APS. Despite antithrombotic treatment, 29% of the patients had further thrombotic events. Five patients (10%) died during the follow-up period, highlighting the seriousness of APS.

Erkan et al (138) analyzed the functional outcome of 39 patients with primary APS after a 10-year follow-up. The authors found that the functional prognosis of this group of very young patients (mean age at diagnosis 27 years) was poor. One-third of patients had organ damage and one fifth were unable to perform activities of daily life.

We describe 16 cases (11 with SLE and 5 with LLD) who developed clinical and/or serologic features of a ‘‘new’’ autoimmune disease after long-term follow-up and 1 patient who developed features of myasthenia gravis. Several studies have suggested that some patients with primary APS may go on to develop characteristics of SLE. To date, there are about 30 reported cases of patients whose primary APS evolved into SLE or LLD (22, 136, 148, 153-157). The percentage of progression to SLE or LLD (21.4%) observed in pediatric patients (22) followed for a median of 6 years is almost double that found in our series of adult patients with primary APS.

APS has extedended into other pro-thrombotic scenarios, such as malignant processes. Trousseau in 1865 (158) first drew attention to thrombotic occlusions in patients with carcinoma and a variety of pathogenic factors have been implicated in the association. There has been experimental work demonstrating tumor growth with agents activating blood coagulation and regression with coagulation inhibitors. Fibrin generation has also been associated with accelerated tumor growth and tumor cells themselves may be responsible for the production of compounds resulting in this mechanism of thrombosis (85). Thromboembolic episodes are not uncommon in some solid tumors (e.g., brain, pancreatic, lung, breast, ovary, renal, etc), although the prevalence in hematological malignancies is lower than that reported for solid tumors. Thrombotic events are increasingly being reported in patients with acute leukemia and chronic myeloproliferative and lymphoproliferative disorders.

There are limited data on whether patients with primary APS have an increased risk of developing cancer as occurs in other systemic autoimmune diseases (e.g., SLE, pSS, RA, or dermatomyositis) (159). In 1984, Finazzi et al (160), evaluated 360 patients with aPL (primary APS in 207, SLE in 112) who were followed for 5 years with regular 6-monthly examinations. They reported that after 4 years of follow-up, 4 patients with primary APS developed a malignant disease [1 breast carcinoma and 3 non- Hodgkin lymphoma (NHL)], result in an estimated rate of 0.28% patient/year, a far higher incidence of NHL than its incidence in the general Western population. Five out of 18 patients who died during the follow-up period had developed haematological malignancies. Miesbach et al (88) retrospectively described the thrombotic manifestations in 58 patients with aPL and a history of neoplasia (39 patients with solid tumors and 19 with hematological malignancies). The pathological significance of aPL in patients with malignancies is, however, still unclear. It has not been established whether the presence of aPL may be considered as an

"epiphenomenon" of the malignant disease or whether it contributes directly to the development of thrombosis in these patients. In the study by Miesbach and colleagues, over a period of 4 years, a history of malignancy was found in 58 out of 425 aPL-positive patients (7%), confirming that underlying malignancy is an important cause of APS.

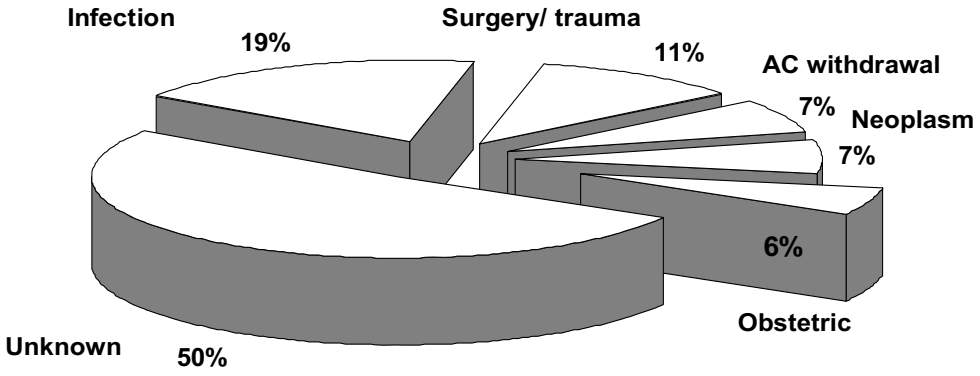
In 29 out of our 120 cases, malignancies were diagnosed after the thrombotic manifestation of APS. Since the publication of our series of patients with malignancies and APS, new cases with primary APS who evolved to a malignancy (one hairy cell leukemia and one Waldenstrom's macroglobulinaemia) have been reported (161,162).

In APS associated with autoimmune diseases or chronic infections, aPL tites wax and wane over time, but do not usually disappear. This situation seems different in APS associated with cancer, where, in a substantial number of patients (around one-third), aPL disappear after correct treatment of the malignancy.

Interestingly, in 17 cases, the malignancy process was the trigger for the development of a CAPS event. The CAPS Registry shows that at least 60% of patients appear to have developed CAPS following an identifiable "trigger" factor. The main precipitating factors are illustrated in Figure 3.

We focused on this aspect and analyzed 15 cases from the "CAPS Registry" who developed a CAPS event during pregnancy and the puerperium. The most characteristic feature of the obstetric APS is pregnancy loss. Recurrent pregnancy loss is a potentially treatable condition when it is associated with aPL. Additionally, a large number of other serious obstetric complications have been related to APS, including preeclampsia, fetal growth restriction, uteroplacental insufficiency, fetal distress and medically induced preterm delivery (163).

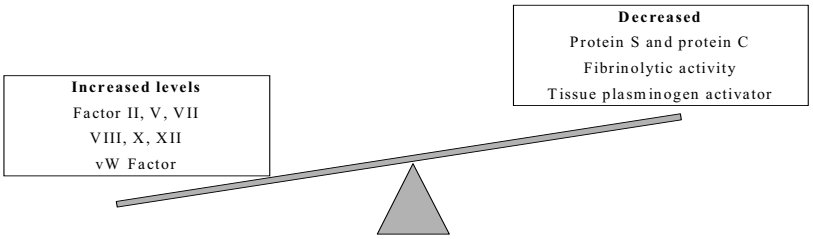
Figure 3. CAPS triggers



Recently, Chakravarty et al (164) estimated the rates of pregnancy outcomes in different autoimmune diseases, including SLE, RA and APS. Based on data from the USA Nationwide Inpatient Sample, the authors estimated that women with APS had an increased risk of hypertensive disorders, intrauterine growth restriction and cesarean delivery in comparison with healthy pregnant controls.

Pregnancy is a well-recognized hypercoagulable state that encompasses a period of 10 to 11 months (including the puerperium). This hypercoagulability is explained by many factors, including alterations in coagulation proteins (increased levels of factors II, V, VII, VIII, X and XII and von Willebrand factor and decreased levels of protein S and activated protein C), alterations in fibrinolytic systems (low plasma fibrinolytic activity during pregnancy, labor and delivery) with reduced activity of tissue plasminogen activator (Figure 4) (165,166). The presence of micro-particles derived from maternal endothelial cells, platelets and placental trophoblasts may also contribute to procoagulant situation.

Figure 4. Abnormalities in coagulation during pregnancy and the puerperium.



VW factor: von Willebrand factor proteins

The risk of venous thrombosis is 5 to 6-fold higher during pregnancy than in non-pregnant women of similar age. Women with previous DVT have an approximately 3.5-fold increased risk of recurrent DVT during pregnancy compared to non-pregnant periods (163).

The main clinical thrombotic characteristics of our patients did not differ from non-pregnant patients with CAPS. Multiorgan involvement with renal, pulmonary, cerebral and intraabdominal thromboses were the most common features. However, there were some specific manifestations, such as HELLP syndrome, placental thrombosis, myometrial TMA or pelvic vein thrombosis. HELLP syndrome was severe (less than 50.000 platelets) in almost all cases. Additionally, the clinical course was unusual in some cases, including persistent thrombocytopenia or early onset HELLP syndrome (during the second trimester).

10. CONCLUSIONS

10.1 Conclusions of the first paper

1. As in APS associated with SLE, the main features of primary APS include pregnancy loss, arterial thrombosis and DVT.
2. Almost two-thirds of patients with CNS involvement present abnormalities on cerebral MRI. Despite anticoagulation treatment, new MRI lesions (mainly ischemic lesions) may appear during follow-up.
3. One-third of patients present cardiac abnormalities (mainly valve lesions) at baseline echocardiography. New valve abnormalities are found during follow-up in spite of anti-thrombotic treatment.
4. After a long-term follow-up, around 10% of the patients with primary APS died, mainly due to PE and cardiovascular events.
5. Our study confirms that progression from primary APS to SLE or LLD is unusual, even after a long follow-up. A positive Coombs test might be a marker for the development of SLE in patients with primary APS.

10.2 Conclusion of the second paper

1 aPL is associated with a wide variety of neoplasms, including solid tumors (mainly, renal cell carcinoma, lung adenocarcinoma and breast cancer) and hematological neoplasms (B-cell lymphoma, spleen lymphoma, chronic myeloid leukemia, among others).

2. Once the malignancy is in remission, aPL may disappear in almost one-third of patients. This particular condition is not usually seen in other “APS scenarios” such as APS associated with SLE or APS associated with chronic infections.
3. Our study suggests that, especially in elderly patients, thrombotic events associated with aPL may be the first manifestation of malignancy. At the same , the presence of

aPL in patients with malignancies has important implications for their treatment and prognosis.

10.3 Conclusions of the third paper

1. Pregnancy and the puerperium are transient hypercoagulable states that predispose to development of thrombosis, especially in those patients with an underlying susceptibility such as APS.
2. APS is associated with several obstetric complications such as recurrent pregnancies losses, preeclampsia, fetal growth restriction, utero-placental insufficiency, fetal distress and preterm delivery.
3. In around 6% of the cases, the CAPS may be present during pregnancy or the puerperium.
4. Patients that present with the CAPS during pregnancy or puerperium have some specific manifestations, such as HELLP syndrome, placental thrombosis, myometrial TMA or pelvic vein thrombosis.
5. The mortality rate in patients presenting CAPS during pregnancy and the puerperium is high in the mother (46%), and in babies (54%).
6. Our results suggest that the possibility of the development of CAPS in patients with signs of HELLP syndrome and multiorgan failure during pregnancy or the puerperium, especially patients with a history of abortions and/or thrombosis, should be borne in mind.

10.4 Final conclusions

Primary APS is a widely recognized distinct entity which rarely progresses to SLE, even after long-term follow-up. APS may also be associated with other chronic disorders, such as solid tumors or hematological malignancies. In cases with the life-threatening variant of APS known as CAPS, pregnancy and the puerperium are periods of high susceptibility for the development of this often fatal form of presentation.

11. REFERENCES

1. Wassermann A, Neisser A, Bruck C. Eine serodiagnostiche reaktion bei syphilis. Dtsch Med Wochenschr 1906;32:745.

2. Pangborn MC. A new serologically active phospholipid from beef heart. Proc Soc Exp Biol 1941;48:484-486.

3. Moore JE, Lutz WB. The natural history of systemic lupus erythematosus: an approach to its study through chronic biologic false positive reactors. J Chronic Dis. 1955;1:297-316

4. Conley CL, Hartman RC. A hemorrhagic disorder caused by circulanting anticoagulant in patients with disseminated lupus erythematosus. J Clin Invest 1952; 31:621-622.

5. Feinstein DI, Rapaport SI. Acquired inhibitors of blood coagulation Prog Hemost Thromb 1972;1:75-95

6. Harris EN, Gharavi AE, Boey ML, Patel BM, Mackworth-Young CG, Loizou S et al. Anticardiolipin antibodies: detection by radioimmunoassay and association with thrombosis in systemic lupus erythematosus. Lancet. 1983;ii:1211-1214.

7. Harris EN, Chan JK, Asherson RA, Aber VR, Gharavi AE, Hughes GR. Thrombosis, recurrent fetal loss, and thrombocytopenia. Predictive value of the anticardiolipin antibody test. Arch Intern Med 1986 ;146:2153-2156.

8. Asherson RA. The catastrophic antiphospholipid syndrome. J Rheumatol 1992;19:508-512.

9. Wilson WA, Gharavi AE, Koike T, Lockshin MD, Branco DW, Piette JC et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. Arthritis Rheum 1999 ;42:1309-1311.

10. Miyakis S, Lockshin MD, Atsumi T, Branco DW, Brey RL, Cervera R et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006;4:295-306.

11. Espinosa G, Cervera R, Font J, Shoenfeld Y. Antiphospholipid syndrome: pathogenic mechanisms. Autoimm Rev 2003; 2: 86-93.

12. Meroni PL, Riboldi P. Pathogenic mechanisms mediating antiphospholipid syndrome. Curr Opin Rheumatol 2001;13:377-382.

13. Salmon JE, Girardi G, Lockshin MD. The antiphospholipid syndrome as a disorder initiated by inflammation: implications for the therapy of pregnant patients. Nat Clin Pract Rheumatol 2007;3:140-147

14. Girardi G, Berman J, Redecha P, Spruce L, Thurman JM, Kraus D et al. Complement C5a receptors and neutrophils mediate fetal injury in the antiphospholipid syndrome. J Clin Invest 2003; 112: 1644–1654

15. Pierangeli SS, Girardi G, Vega-Ostertag M, Liu X, Espinola RG, Salmon J. Requirement of activation of complement C3 and C5 for antiphospholipid antibody-mediated thrombophilia. Arthritis Rheum 2005*;* 52: 2120–2124

16. Asherson RA. A "primary" antiphospholipid syndrome? J Rheumatol. 1988;15:1742-1746.

17. Asherson RA, Khamashta MA, Ordi-Ros J, Derksen RH, Machin SJ, Barquinero J et al. The "primary" antiphospholipid syndrome: major clinical and serological features. Medicine (Baltimore) 1989;68:366-374.

18. Piette JC, Wechsler B, Francis C, Godeau P. Systemic lupus erythematosus and the antiphospholipid syndrome: reflections about the relevance of ARA criteria. J Rheumatol 1992;19:1835-1837.

19. Vianna JL, Khamashta MA, Ordi-Ros J, Font J, Cervera R, Lopez-Soto A et al.

Comparison of the primary and secondary antiphospholipid syndrome: a European Multicenter Study of 114 patients. Am J Med 1994; 96: 3 – 9.

20. Cervera R, Piette JC, Font J, Khamashta MA, Shoenfeld Y, Camps MT et al. Antiphospholipid syndrome: clinical and immunological manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthritis Rheum 2002; 46:1019– 1027.

21. Soltesz P, Veres K, Lakos G, Kiss E, Muszbek L, Szegedi G. Evaluation of clinical and laboratory features of antiphospholipid syndrome: a retrospective study of 637 patients. Lupus 2003;12:302-307.

22. Gattorno M, Falcini F, Ravelli A, Zulian F, Buoncompagni A, Martini G, Resti M, Outcome of primary antiphospholipid syndrome in childhood. Lupus 2003;12:449-453.

23. Espinola-Zavaleta N, Amigo MC, Vargas-Barron J, Keirns C, Cardenas AR, Vidal M, Roldan J. Two- and three-dimensional echocardiography in primary antiphospholipid syndrome: misdiagnosis as rheumatic valve disease. Lupus 2001;10:511-513

24. Uthman I, Khamashta MA. Ethnic and geographical variation in antiphospholipid (Hughes) syndrome. Ann Rheum Dis 2005;64;1671-1676.

25. Goldstein R, Moulds JM, Smith CD, Sengar DP. MHC studies of the primary antiphospholipid antibody syndrome and of antiphospholipid antibodies in systemic lupus erythematosus. J Rheumatol 1996;23:1173–1179.

26. Freitas MV, da Silva LM, Deghaide NH, Donadi EA, Louzada-Junior P. Is HLA class II susceptibility to primary antiphospholipid syndrome different from susceptibility to secondary antiphospholipid syndrome? Lupus 2004;13:125–131.

27. Caliz R, Atsumi T, Kondeatis E, Amengual O, Khamashta MA, Vaughan RW, et al. HLA class II gene polymorphisms in antiphospholipid syndrome: haplotype analysis in 83 Caucasoid patients. Rheumatology (Oxford) 2001;40:31–36.

28. Krause I, Leibovici L, Brank M, Shoenfeld Y. Clusters of disease manifestations in patients with antiphospholipid syndrome demonstrated by factor analysis. Lupus 2007; 16:176-180.

29. Vila P, Hernandez MC, Lopez-Fernandez MF, Battle J. Prevalence, follow-up and clinical significance of the anticardiolipin antibodies in normal subjects. Thromb Haemost 1994; 72:209-213.

30. Shi W, Krilis SA, Chong BH, Gordon S, Chesterman CN. Prevalence of lupus anticoagulant in a healthy population: Lack of correlation with anticardiolipin antibodies. Aust N Z J Med 1990; 20:231-236.

31. Melk A, Mueller Eckhardt G, Polten B, Lattermann A, Heine O, Hoffmann O. Diagnostic and prognostic significance of anticardiolipin antibodies in patients with recurrent spontaneous abortions. Am J Reprod Immunol 1995; 33:228-233.

32. McNeil HP, Chesterman CN, Krilis SA. Immunology and clinical importance of antiphospholipid antibodies. Adv Immunol 1991; 49:193-280.

33. Sebastiani GD, Galeazzi M, Tincani A, Piette JC; Font J, Allegri F et al. Anticardiolipin and anti-beta2GPI antibodies in a large series of European patients with systemic lupus erythematosus. Prevalence and clinical associations. European Concerted Action on the Immunogenetics of SLE. Scand J Rheumatol 1999; 28:344-351

34. Cervera R, Asherson RA. Clinical and epidemiological aspects in the antiphospholipid syndrome. Immunobiology 2003; 207:5-11

35. Bidot CJ, Jy W, Horstman LL, Ahn ER, Yaniz M, Ahn YS. Antiphospholipid antibodies (APLA) in immune thrombocytopenic purpura (ITP) and antiphospholipid syndrome (APS). Am J Hematol 2006; 81:391-396.

36. Avcin T, Ambrozic A, Bozic B, Acceto M, Kveder T, Rozman B. Estimation of anticardiolipin antibodies, anti-beta2 glycoprotein I antibodies and lupus anticoagulant in a prospective longitudinal study of children with juvenile idiopathic arthritis. Clin Exp Rheumatol 2002 ;20:101-108.

37. Olech E, Merrill JT. The prevalence and clinical significance of antiphospholipid antibodies in rheumatoid arthritis. Curr Rheumatol Rep 2006;8:100-108.

38. Buchanan RR, Wardlaw JR, Riglar AG, Littlejohn GO, Miller MH. Antiphospholipid antibodies in the connective tissue diseases: their relation to the antiphospholipid syndrome and forme fruste disease. J Rheumatol 1989;16:757-761.

39. Picillo U, Migliaresi S, Marcialis MR, Ferruzzi AM, Tirri G. Clinical significance of anticardiolipin antibodies in patients with systemic sclerosis. Autoimmunity 1995; 20:1-7.

40. Tokay S, Direskeneli H, Yurdakul S, Akoglu T. Anticardiolipin antibodies in Behcet's disease: a reassessment. Rheumatology (Oxford) 2001; 40:192-195

41. Fauchais AL, Lambert M, Launay D, Michon-Pasturel U, Queyrel V, Nguyen N et al. Antiphospholipid antibodies in primary Sjogren's syndrome: prevalence and clinical significance in a series of 74 patients. Lupus 2004; 13:245-248

42. Ramos-Casals M, Nardi N, Brito-Zerón P, Aguiló S, Gil V, Delgado G et al. Atypical autoantibodies in patients with primary Sjogren syndrome: clinical characteristics and follow-up of 82 cases. Semin Arthritis Rheum 2006;35:312-321.

43. Komatireddy GR, Wang GS, Sharp GC, Hoffman RW. Antiphospholipid antibodies among anti-U1-70 kDa autoantibody positive patients with mixed connective tissue disease. J Rheumatol 1997;24:319-322.

44. Sherer Y, Livneh A; Levy Y, Shoenfeld Y, Langevitz P. Dermatomyositis and polymyositis associated with the antiphospholipid syndrome-a novel overlap syndrome. Lupus 2000;9:42-46.

45. Chakravarty K, Pountain G, Merry P, Byron M, Hazleman B, Scott DG. A longitudinal study of anticardiolipin antibody in polymyalgia rheumatica and giant cell arteritis. J Rheumatol 1995; 22:1694-1697.

46. Ruffatti, A, Veller-Fornasa C, Patrassi GM Sartori E, Tonello M, Tonetto S et al. Anticardiolipin antibodies and antiphospholipid syndrome in chronic discoid lupus erythematosus. Clin Rheumatol 1995; 14:402-404

47. Carreira, PE, Montalvo MG, Kaufman LD, Silver RM, Izquierdo M, Gómez-Reino JJ et al. Antiphospholipid antibodies in patients with eosinophilia myalgia and toxic oil syndrome. J Rheumatol 1997; 24:69-2472

48. Rees JD, Lanca S, Marques PV, Gómez Puerta JA, Moco R, Oliveri C et al. Prevalence of the antiphospholipid syndrome in primary systemic vasculitis. Ann Rheum Dis 2006;65:109-111.

49. Nabriski D, Ellis M, Ness-Abramof R, Shapiro M, Shenkman L. Autoimmune thyroid disease and antiphospholipid antibodies. Am J Hematol 2000;64:73-75.

50. Triplett DA. Many faces of lupus anticoagulants. Lupus 1998; 7 Suppl 2:S18-22.

51. Merrill JT, Shen C, Gugnani M Lahita RG, Mongey AB. High prevalence of antiphospholipid antibodies in patients taking procainamide. J Rheumatol 1997; 24:1083-1088.

52. Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P, et al. Systemic lupus erythematosus: clinical and immunologic patterns of disease expression in a cohort of 1,000 patients. Medicine (Baltimore) 1993;72:113–124.

53. Petri M. Clinical and management aspects of the antiphospholipid syndrome. In Dubois' Lupus Erythematosus, 5th edn. D.J. Wallace, B.H. Hahn, eds. Williams & Wilkins, Baltimore, 1997; pp 57-69

54. Love PE, Santoro SA. Antiphospholipid antibodies, anticardiolipin and the lupus anticoagulant in systemic lupus erythematosus (SLE) and in non-SLE disorders. Ann Intern Med 1990;112: 682–689

55. McClain MT, Arbuckle MR, Heinlen LD, Dennis GJ, Roebuck J, Rubertone MV, Harley JB, James JA. The prevalence, onset, and clinical significance of antiphospholipid antibodies prior to diagnosis of systemic lupus erythematosus. Arthritis Rheum 2004;50:1226-1232.

56. Williams FMK, Chinn S, Hughes GRV, Leach RM. Critical illness in systemic lupus erythematosus and the antiphospholipid syndrome. Ann Rheum Dis 2002;61:414–421

57. Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P et al. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. Medicine (Baltimore) 2003 ;82:299-308.

58. Khamashta MA, Cervera R, Asherson RA, Font J, Gil A, Coltart DJ et al. Association of antibodies against phospholipids with heart valve disease in systemic lupus erythematosus. Lancet 1990;335:1541–1544.

59. Manzi S, Meilahn EN, Rairie JE, Conte CG, Medsger TA Jr, Jansen-McWilliams L, D'Agostino RB, Kuller LH. Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the Framingham Study. Am J Epidemiol 1997;145:408-415

60. Mackworth-Young CG, Hughes GRV. Epilepsy: an early symptom of systemic lupus erythematosus. J Neurol Neurosurg Psychiatry 1985;48:185.

61. Herranz MT, Rivier G, Khamashta MA, Blaser KU, Hughes GRV. Association between antiphospholipid antibodies and epilepsy in patients with systemic lupus erythematosus. Arthritis Rheum 1994;37:568–571.

62. Denburg SD, Carbotte RM, Ginsberg JS, Denburg JA. The relationship of antiphospholipid antibodies to cognitive function in patients with systemic lupus erythematosus. J Int Neuropsychol Soc 1997;3:377–386.

63. Gómez-Puerta JA, Cervera R, Calvo LM, Gómez-Ansón B, Espinosa G, Claver G et al. Dementia associated with the antiphospholipid syndrome: clinical and radiological characteristics of 30 patients. Rheumatology (Oxford) 2005;44:95-99.

64. Forman JP, Lin J, Pascual M, Denton MD, Tolkoff-Rubin N. Significance of anticardiolipin antibodies on short and long term allograft survival and function following kidney transplantation. Am J Transplant 2004;4:1786-1791.

65. Stone JH, Amend WJ, Criswell LA. Antiphospholipid antibody syndrome in renal transplantation: occurrence of clinical events in 96 consecutive patients with systemic lupus erythematosus. Am J Kidney Dis 1999;34:1040-1047.

66. Radhakrishnan J, Williams GS, Appel GB, Cohen DJ. Renal transplantation in anticardiolipin antibody-positive lupus erythematosus patients. Am J Kidney Dis 1994;23:286-289.

67. Fernandez-Fresnedo G, Lopez-Hoyos M, Segundo DS, Crespo J, Ruiz JC, De Francisco AL, Arias M. Clinical significance of antiphospholipid antibodies on allograft and patient outcome after kidney transplantation. Transplant Proc 2005;37:3710-3711.

68. Espinosa G, Cervera R, Font J, Asherson RA. The lung in the antiphospholipid syndrome. Ann Rheum Dis 2002;61:195–198

69. Alarcón-Segovia D, Deleze M, Oria CV, Sánchez-Guerrero J, Gómez-Pacheco L, Cabiedes J, et al. Antiphospholipid antibodies and the antiphospholipid syndrome in systemic lupus erythematosus. A prospective analysis of 500 consecutive patients. Medicine (Baltimore) 1989;68:353–365.

70. Erkan D. Lupus and thrombosis. J Rheumatol 2006;33:1715-1717

71. Asherson RA, Cervera R. Antiphospholipid antibodies and infections. Ann Rheum Dis 2003;62:388–393

72. Blank M, Krause I, Fridkin M, Keller N, Kopolovic J, Goldberg I, et al. Bacterial induction of autoantibodies to b2-glycoprotein-1 accounts for the infectious etiology of antiphospholipid syndrome. J Clin Invest 2002;109:797–804.

73. Cervera R, Asherson RA, Acevedo ML, Gómez-Puerta JA, Espinosa G, De La Red G et al. Antiphospholipid syndrome associated with infections: clinical and microbiological characteristics of 100 patients. Ann Rheum Dis 2004; 63:1312-1317.

74. Uthman IW, Gharavi AE. Viral infections and antiphospholipid antibodies. Semin Arthritis Rheum 2002;31:256-263.

75. Ramos-Casals M, Cervera R, Lagrutta M, Medina F, Garcia-Carrasco M, de la Red G et al. Clinical features related to antiphospholipid syndrome in patients with chronic viral infections (hepatitis C virus/HIV infection): description of 82 cases. Clin Infect Dis. 2004;38:1009-1116

76. Galrao L, Brites C, Atta ML, Atta A, Lima I, Gonzalez F et al. Antiphospholipid antibodies in HIV-positive patients. Clin Rheumatol. 2007 Feb 28; [Epub ahead of print]

77. Asherson RA, Gómez-Puerta JA, Marinopoulos G. Recurrent pulmonary thromboembolism in a patient with systemic lupus erythematosus and HIV-1 infection

associated with the presence of antibodies to prothrombin: a case report. Clin Inf Dis 2005; 41:e89–92

78. Arvieux J, Darnige L, Reber G, Bensa JC, Colomb MG. Development of an ELISA for autoantibodies to prothrombin showing their prevalence in patients with lupus anticoagulants. Thromb Haemost 1995; 74:1120–1125.

79. Rojas-Rodrıguez J, Garcıa-Carrasco M, Ramos-Casals M, Enriquez- Coronel G, Colchero C, Cervera R, et al. Catastrophic antiphospholipid syndrome: clinical description and triggering factors in 8 patients. J Rheumatol 2000;27:238–40.

80. Fernandez RLF, Gil JG. Anticardiolipin antibodies and polyarteritis nodosa. Lupus 1994;3:523–524.

81. Handa R, Aggarwal P, Biswas A, Wig N, Wali JP. Microscopic polyangiitis associated with antiphospholipid syndrome. Rheumatology (Oxford) 1999;38:478–479.

82. Castellino G, La Corte R, Santilli D, Trotta F. Wegener's granulomatosis associated with antiphospholipid syndrome. Lupus 2000;9:717–720.

83. Manna R, Latteri M, Cristiano G, Todaro L, Scuderi F, Gasbarrini G. Anticardiolipin antibodies in giant cell arteritis and polymyalgia rheumatica: a study of 40 cases. Br J Rheumatol 1998;37:208–210

84. Hull R, Harris E, Gharavi A, Tincani A, Asherson RA, Valesini G, et al. Anticardiolipin antibodies: occurrence in Behçet's syndrome. Ann Rheum Dis 1984;43:746–748.

85. Asherson RA. Antiphospholipid antibodies, malignancies and paraproteinemias. J Autoimmun. 2000 15:117-122.

86. Schved JF, Dupuy-Fons C, Biron C, Quere I, Janbon C. A prospective epidemiological study on the occurrence of antiphospholipid antibody: the Montpellier Antiphospholipid (MAP) Study. Haemostasis 1994;24:175-182

87. Zuckerman E, Toubi E, Golan TD, Rosenvald-Zuckerman T, Shmuel Z, Yeshurun D. Increased thromboembolic incidence in anti-cardiolipin-positive patients with malignancy. Br J Cancer 1995;72:447-451.

88. Miesbach W, Scharrer I, Asherson R. Thrombotic manifestations of the antiphospholipid syndrome in patients with malignancies. Clin Rheumatol. 2006;25:840-844.

89. Fort JG, Cowchock FS, Abruzzo RL, Smith JB. Anticardiolipin antibodies in patients with rheumatic diseases. Arthritis Rheum 1987;30:752–760

90. Keane A, Woods R, Dowding V, Roden D, Barry C. Anticardiolipin antibodies in rheumatoid arthritis. Br J Rheumatol 1987;26:346–350.

91. Wolf P, Gretler J, Aglas F, Auer-Grumbach P, Rainer F. Anticardiolipin antibodies in rheumatoid arthritis: their relation to rheumatoid nodules and cutaneous vascular manifestations. Br J Dermatol 1994;131:48–51

92. Merkel PA, Chang YC, Pierangeli SS, Convery K, Harris N, Polisson RP. The prevalence and clinical associations of anticardiolipin antibodies in a large inception cohort of patients with connective tissue diseases. Am J Med 1996;101:576–583

93. Bonnet C, Vergne P, Bertin P, Treves R, Jauberteau MO. Antiphospholipid antibodies and RA: presence of beta2GP1 independent aCL. Ann Rheum Dis 2001;60:303-304

94. Pahor A, Hojs R, Holc I, Ambrozic A, Cucnik S, Kveder T, Rozman B. Antiphospholipid antibodies as a possible risk factor for atherosclerosis in patients with rheumatoid arthritis. Immunobiology 2006;211:689-694

95. Sherer Y, Gerli R, Vaudo G, Schillaci G, Gilburd B, Giordano A et al. Prevalence of antiphospholipid and antioxidized low-density lipoprotein antibodies in rheumatoid arthritis. Ann N Y Acad Sci. 2005 ;1051:299-303.

96. Seriolo B, Accardo S, Garnero A, Fasciolo D, Cutolo M. Anticardiolipin antibodies, free protein S levels and thrombosis: a survey in a selected population of rheumatoid arthritis patients. Rheumatology (Oxford) 1999;38:675-678

97. Atzeni F, Turiel M, Capsoni F, Doria A, Meroni P, Sarzi-Puttini P. Autoimmunity and anti-TNF-alpha agents. Ann N Y Acad Sci 2005 ;1051:559-569

98. Ferraccioli GF, Mecchia F, Di Poi E, Fabris M. Anticardiolipin antibodies in rheumatoid patients treated with etanercept or conventional combination therapy: direct and indirect evidence for a possible associations with infections. Ann Rheum Dis 2002;61:358–361.

99. Bobbio-Pallavicini F, Alpini C, Caporali R, Avalle S, Bugatti S, Montecucco C. Autoantibody profile in rheumatoid arthritis during long-term infliximab treatment. Arthritis Res Ther 2004;6:R264-272.

100. Cervera R, García-Carrasco M, Font J, Ramos-Casals M, Reverter JC, Muñoz FJ et al. Antiphospholipid antibodies in primary Sjögren syndrome: prevalence and clinical significance in a series of 80 patients. Clin Exp Rheumatol 1997;15:361-365

101. Pennec YL, Magadur G, Jouquan J, Youinou P. Serial measurements of anticardiolipin antibodies in primary Sjögren's syndrome. Clin Exp Rheumatol 1991;9:165-167.

102. Asherson RA, Fei HM, Staub HL, Khamashta MA, Hughes GR, Fox RI. Antiphospholipid antibodies and HLA associations in primary Sjogren's syndrome. Ann Rheum Dis 1992;51:495-498.

103. Jedryka-Goral A, Jagiello P, D'Cruz DP, Maldykowa H, Khamashta MA, Hughes GR, et al. Isotype profile and clinical relevance of anticardiolipin antibodies in Sjogren's syndrome. Ann Rheum Dis 1992;51:889- 891.

104. Parodi A, Drosera M, Barbieri L, Rebora A. Antiphospholipid antibody system in systemic sclerosis. Rheumatology (Oxford) 2001;40:111–112

105. Sanna G, Bertolaccini ML, Mameli A, Hughes GR, Khamashta MA, Mathieu A. Antiphospholipid antibodies in patients with scleroderma: prevalence and clinical significance. Ann Rheum Dis 2005; 64:1795-1796

106. Asherson RA, Cervera R, Piette JC, Font J, Lie JT, Borcoglu A, et al. Catastrophic antibody syndrome. Clinical and laboratory features of 50 patients. Medicine (Baltimore) 1998;77:195-207.

107. Asherson RA, Cervera R, Piette JC, Shoenfeld Y, Espinosa G, Petri MA, et al. Catastrophic antiphospholipid syndrome: Clues to the pathogenesis from a series of 80 patients. Medicine (Baltimore) 2001; 80: 355-376.

108. Asherson RA, Cervera R, de Groot PG, Erkan D, Boffa MC, Piette JC et al. Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines. Lupus 2003;12:530-534.

109. Cervera R, Font J, Gómez-Puerta JA, Espinosa G, Cucho M, Bucciarelli S, et al. Validation of the preliminary criteria for the classification of catastrophic antiphospholipid syndrome. Ann Rheum Dis 2005; 64: 1205-1209.

110. Cervera R, Asherson RA. Catastrophic antiphospholipid syndrome. Rheum Dis Clin North Am 2006;32:575-590

111. Bucciarelli S, Espinosa G, Asherson RA, Cervera R, Claver G, Gómez-Puerta JA, et al. The acute respiratory distress syndrome in catastrophic antiphospholipid syndrome: analysis of a series of 47 patients. Ann Rheum Dis 2006; 65: 81-86.

112. Asherson RA, Espinosa G, Cervera R, Gómez-Puerta JA, Musuruana J, Bucciarelli S, et al. Disseminated intravascular coagulation in catastrophic antiphospholipid syndrome:

clinical and haematological characteristics of 23 patients. Ann Rheum Dis 2005; 64: 943-946.

113. Bucciarrelli S. Espinosa G, Cervera R, Erkan D, Gómez-Puerta JA, Ramos-Casals M et al. Mortality in the catastrophic antiphospholipid syndrome: causes of death and prognostic factors in a series of 250 patients. Arthritis Rheum 2006;54:2568-2576

114. Bayraktar UD, Erkan D, Bucciarelli S, Espinosa G, Asherson RA. The clinical spectrum of catastrophic antiphospholipid syndrome in the absence and presence of lupus. J Rheumatol 2007;34:346-352

115. Erkan D, Asherson RA, Espinosa G, Cervera R, Font J, Piette JC, et al. The long-term outcome of catastrophic antiphospholipid syndrome survivors. Ann Rheum Dis 2003; 62: 530-533.

116. Lockshin MD, Erkan D. Treatment of the antiphospholipid syndrome. N Engl J Med 2003;349:1177-9.

117. Khamashta MA. Primary prevention of thrombosis in subjects with positive antiphospholipid antibodies. J Autoimmun 2000;15:249-253

118. Wallace D.J., Linker-Israeli M., Metzger A.I., Stecher V.J. The relevance of antimalarial therapy with regard to thrombosis, hypercholesterolemia and cytokines in SLE. Lupus 1993: 2(Suppl.): S13–S15

119. Petri M. Hydroxychloroquine use in the Baltimore lupus cohort: effects on lipids, glucose and thrombosis. Lupus 1996*;* 5(Suppl.): S16–S22

120. Empson M, Lassere M, Craig J, Scott J. Prevention of recurrent miscarriage for women with antiphospholipid antibody or lupus anticoagulant. Cochrane Database Syst Rev 2005;2: CD002859.

121. Lim W, Crowther MA, Eikelboom JW. Management of antiphospholipid antibody syndrome: a systematic review. JAMA 2006;295:1050-1057

122. Khamashta MA, Cuadrado MJ, Mujic F, Taub NA, Hunt BJ, Hughes GR. The management of thrombosis in the antiphospholipid-antibody syndrome. N Engl J Med 1995;332:993-997.

123. Muñoz-Rodriguez FJ, Font J, Cervera R, Reverter JC, Tàssies D, Espinosa G, et al. Clinical study and follow-up of 100 patients with the antiphospholipid syndrome. Semin Arthritis Rheum 1999;29:182-90.

124. Ruiz-Irastorza G, Khamashta MA, Hunt BJ, Escudero A, Cuadrado MJ, Hughes GR. Bleeding and recurrent thrombosis in definite antiphospholipid syndrome: analysis of a series of 66 patients treated with oral anticoagulation to a target international normalized ratio of 3.5. Arch Intern Med 2002;162:1164-1169.

125. Vaidya S, Sellers R, Kimball P, Shanahan T, Gitomer J, Gugliuzza K, et al. Frequency, potential risk and therapeutic intervention in end-stage renal disease patients with antiphospholipid antibody syndrome: a multicenter study. Transplantation 2000;69:1348-1352.

126. Crowther MA, Ginsberg JS, Julian J, Denburg J, Hirsh J, Douketis J, et al. A comparison of two intensities of warfarin for the prevention of recurrent thrombosis in patients with the antiphospholipid antibody syndrome. N Engl J Med 2003;349:1133-1138.

127. Finazzi G, Marchioli R, Brancaccio V, Schinco P, Wisloff F, Musial J, et al. A randomized clinical trial of high-intensity warfarin vs. conventional antithrombotic therapy for the prevention of recurrent thrombosis in patients with the antiphospholipid syndrome (WAPS). J Thromb Haemost 2005;:848-853.

128. Rivier G, Herranz MT, Khamashta MA, Hughes GR. Thrombosis and antiphospholipid syndrome: a preliminary assessment of three antithrombotic treatments. Lupus 1994;3:85-90.

129. Rosove MH, Brewer PM. Antiphospholipid thrombosis: clinical course after the first thrombotic event in 70 patients. Ann Intern Med 1992;117:303-308.

130. Bertsias GK, Ioannidis JP, Boletis J, Bombardieri S, Cervera R, Dostal C et al. EULAR recommendations for the management of Systemic Lupus Erytematosus (SLE) Report of a Task Force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT)* Ann Rheum Dis. 2007 May 15; [Epub ahead of print].

131. Espinosa G, Tàssies D, Reverter JC. Hematological abnormalities in the antiphospholipid syndrome. In The Antiphospholipid Syndrome II: Autoimmune thrombosis. Ed. Asherson RA, Cervera R, Piette JC, Shoenfeld Y. Elsevier 2002; pp 259-283.

132. Sibai BM, Taslimi MM, el Nazer A, Amon E, Mabie BC, Ryan GM. Maternal-perinatal outcome associated with the syndrome of hemolysis, elevated liver enzymes, and low platelets in severe preeclampsia-eclampsia. Am J Obstet Gynecol 1986;155:501-509.

133. Martin JN Jr, Rinehart BK, May WL, Magann EF, Terrone DA, Blake PG. The spectrum of severe preeclampsia: comparative analysis by HELLP (hemolysis, elevated liver enzyme levels, and low platelet count) syndrome classification. Am J Obstet Gynecol 1999;180:1373-1384

134. Hughes GRV. Thrombosis, abortion, cerebral disease, and the lupus anticoagulant. Br J Med (Clin Res Ed). 1983;287:1088–1089.

135. Harris EN, Pierangeli SS. Primary, Secondary, Catastrophic Antiphospholipid Syndrome: is there a difference? Thromb Res. 2004;114:357-361.

136. Mujic F, Cuadrado MJ, Lloyd M, Khamashta MA, Page G, Hughes GRV. Primary antiphospholipid syndrome evolving into systemic lupus eryhtematosus. J Rheumatol. 1995;22:1589–1592.

137. Muñoz-Rodriguez FJ, Font J, Cervera R, Reverter JC, Tassies D, Espinosa G, López-Soto A, Carmona F, Balasch J, Ordinas A, Ingelmo M. Clinical study and follow-up of 100 patients with the antiphospholipid syndrome. Semin Arthritis Rheum 1999;29:182–190

138. Erkan D, Yazici Y, Sobel R, Lockshin MD. Primary antiphospholipid syndrome: functional outcome after 10 years. J Rheumatol 2000;27: 2817–2821.

139. Girón-González JA, Garcia del Río E, Rodríguez C, Rodríguez-Martorell J, Serrano A. Antiphospholipid syndrome and asymptomatic carriers of antiphospholipid antibody: prospective analysis of 404 individuals. J Rheumatol. 2004;31:1560-1567

140. Medina G, Vera-Lastra O, Barile L, Salas M, Jara LJ. Clinical spectrum of males with primary antiphospholipid syndrome and systemic lupus erythematosus: a comparative study of 73 patients. Lupus 2004;13:11-16.

141. Krause I, Blank M, Fraser A, Lorber M, Stojanovich L, Rovensky J, Shoenfeld Y. The association of thrombocytopenia with systemic manifestations in the antiphospholipid syndrome. Immunobiology 2005;210:749-754.

142. Sanna G, Bertolaccini ML, Cuadrado MJ, Laing H, Khamashta MA, Mathieu A, Hughes GR. Neuropsychiatric manifestations in systemic lupus erythematosus: prevalence and association with aPL. J Rheumatol. 2003;30:985–992.

143. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med. 2003;348:1215–1222.

144. Tektonidou MG, Varsou N, Kotoulas G, Antoniou A, Moutsopoulos HM. Cognitive deficits in patients with antiphospholipid syndrome: association with clinical, laboratory, and brain magnetic resonance imaging findings. Arch Intern Med. 2006;166:2278-2284.

145. Cuadrado MJ, Khamashta MA, Ballesteros A, Godfrey T, Simon MJ, Hughes GRV. Can neurologic manifestations of Hughes (antiphospholipid) syndrome be distinguished from multiple sclerosis? Analysis of 27 patients and review of the literature. Medicine (Baltimore) 2000;79: 57–68.

146. Turiel M, Sarzi-Puttini P, Peretti R, Bonizzato S, Muzzupappa S, Atzeni F, Rossi E, Doria A. Five-year follow-up by transesophageal echocardiographic studies in primary antiphospholipid syndrome. Am J Cardiol 2005;96:574-579.

147. Branch DW, Silver RM, Blackwell JL, Reading JC, Scott JR. Outcome of treated pregnancies in women with antiphospholipid syndrome: an update of the Utah experience. Obstet Gynecol 1992;80:614–620.

148. Carbone J, Orera M, Rodríguez-Mahou M, Rodriguez-Perez C, Sanchez-Ramon S, Seoane E et al. Immunological abnormalities in primary APS evolving into SLE: 6 years follow-up in women with repeated pregnancy loss. Lupus 1999;8:274–278.

149. Rottem M, Krause I, Fraser A, Stojanovich L, Rovensky J, Shoenfeld Y. Autoimmune hemolytic anaemia in the antiphospholipid syndrome. Lupus. 2006;15:473-477.

150. Reshetnyak TM, Alekberova ZS, Kalashnikova LA, Alexandrova EN, Mach ES, Radenska-Lopovok SG et al. Survival and prognostic factors of death risk in antiphospholipid syndrome: 8 year follow-up. Ter Arkh 2003;75:46–51.

151. Ruiz-Irastorza G, Egurbide MV, Ugalde J, Aguirre C. High impact of antiphospholipid syndrome on irreversible organ damage and survival of patients with systemic lupus erythematosus. Arch Intern Med 2004;164:77-82.

152. Shah NM, Khamashta MA, Atsumi T, Hughes GR. Outcome of patients with anticardiolipin antibodies: a 10 year follow-up of 52 patients. Lupus 1998;7:3-6.

153. Asherson RA, Baguley E, Pal C, Hughes GRV. Antiphospholipid syndrome: five years follow up. Ann Rheum Dis. 1991;50:805–810.

154. Blanco Y, Ramos-Casals M, Garcia-Carrasco M, Cervera R, Font J, Ingelmo M. Sindrome antifosfolipidico primario que evoluciona a lupus eritematoso sistemico: presentacion de tres nuevos casos y revision de la literatura. Rev Clin Esp. 1999;199:586–588.

155. Derksen RHWM, Gmelig-Meijling FHJ, de Groot PG. Primary antiphospholipid syndrome evolving into systemic lupus erythematosus. Lupus. 1996;5:77–80.

156. Queiro R, Weruaga A, Riestra JL. C4 deficiency state in antiphospholipid antibody-related recurrent preeclampsia evolving into systemic lupus erythematosus. Rheumatol Int. 2002;22:126–128.

157. Seisedos L, Muñoz-Rodriguez FJ, Cervera R, Font J, Ingelmo M. Primary antiphospholipid syndrome evolving into systemic lupus erythematosus. Lupus 1997;6:285–286.

158. Trousseau A. Phlegmasia alba dolens Clinique Medical de L'Hotel- Dieu de Paris, Vol. 3. The New Sydenham Society, London, 1865; p 94.

159. Naschitz JE, Rosner I, Rozenbaum M, Zuckerman E, Yeshurun D. Rheumatic syndromes: clues to occult neoplasia. Semin Arthritis Rheum 1999;29:43-55.

160. Finazzi G, Brancaccio V, Moia M, Ciaverella N, Mazzucconi MG, Schinco PC, et al. Natural history and risk factors for thrombosis in 360 patients with antiphospholipid

antibodies: a four-year prospective study from the Italian Registry. Am J Med 1996;100:530-536.

161. Diz-Kucukkaya R, Dincol G, Kamali S, Kural F, Inanc M. Development of hairy cell leukemia in a patient with antiphospholipid syndrome. Lupus 2007;16:286-8.

162. Asherson RA, Davidge-Pitts MC, Wypkema E. Primary" antiphospholipid syndrome evolving into Waldenstrom's macroglobulinaemia: a case report. Clin Rheumatol 2007;26:278-280.

163. Gómez-Puerta JA, Cervera R, Espinosa G, Bucciarelli S, Font J. Pregnancy and puerperium are high susceptibility periods for the development of catastrophic antiphospholipid syndrome. Autoimmun Rev 2006;6:85-88

164. Chakravarty EF, Nelson L, Krishnan E. Obstetric hospitalizations in the United States for women with systemic lupus erythematosus and rheumatoid arthritis. Arthritis Rheum 2006;54:899-907.

165. Brenner B. Haemostatic changes in pregnancy. Thromb Res 2004;114:409-14

166. Toglia MR, Weg JG. Venous thromboembolism during pregnancy. N Engl J Med 1996;335:108-114.

APPENDIX I: SUMMARY IN SPANISH

INTRODUCCIÓN

El síndrome antifosfolipídico (SAF) es una enfermedad autoinmune caracterizada por trombosis venosas o arteriales recurrentes, pérdidas fetales (usualmente recurrente o muerte fetal intrauterina) y trombocitopenia asociadas con la presencia de los anticuerpos antifosfolipídicos (AAF) incluyendo fundamentalmente los anticuerpos anticardiolipina (aCL) y el anticoagulante lúpico (AL) los cuales se dirigen contra la proteína de unión fosfolipídica, la ß2glicoprotéina 1 ($ß_2$GPI) y contra la protombina. Hace casi cien años se describieron las primeras pruebas reagínicas como técnicas de detección de infecciones treponémicas, las cuales se fueron perfeccionando a lo largo del siglo pasado y permitieron reconocer a algunos pacientes que presentaban falsa positividad de dichas pruebas y desarrollaban enfermedades autoinmunes y trombosis. Así mismo, en los años cincuenta del siglo pasado se describió el fenómeno "anticoagulante lúpico" y se observó que se asociaba en muchas ocasiones a la presencia de serología luética falsamente positiva. Wassermann y cols describieron el primer anticuerpo antifosfolipídico en 1906: la reagina asociada a sífilis (1). En 1952 Conley y Hartmann describen por primera vez la asociación entre un anticoagulante circulante y el LES (4). Pero no fue hasta hace sólo 24 años, que el doctor Graham Hughes describe por primera vez la asociación de manifestaciones trombóticas, abortos, enfermedad neurológica y la presencia de AL como constitutivos de un síndrome no descrito previamente como tal (134). Actualmente se conoce no sólo la asociación del SAF al LES sino también a una serie de procesos tales como las infecciones crónicas (73), las vasculitis sistémicas (48) o las neoplasias (85).

PATOGÉNESIS

Se han propuesto varios mecanismos por los cuales los aCL promueven el desarrollo de trombosis. Los AAF inhiben reacciones en la cascada de la coagulación catalizadas por fosfolípidos cargados negativamente, además presentan interacción entre estos y activadores antigénicos sobre las plaquetas, células endoteliales y componentes de la cascada de la coagulación. Afecta la activación del factor X, la conversión protrombina-trombina, la activación de la proteína C y la inactivación del factor Va induciendo un estado protrombótico. Podría afectar igualmente la síntesis de tromboxano por las plaquetas, inhibiendo la síntesis de prostaciclina y activando células endoteliales que regulan la expresión de moléculas de adhesión, la producción de factores tisulares por células endoteliales como la endotelina-1, la secreción de citoquinas proinflamatorias y la modulación del metabolismo del ácido araquidónico. La hipótesis del segundo "hit" postula que un defecto subyacente endotelial en la presencia de anticuerpos dispara las complicaciones trombóticas (11). La $ß_2$GPI es un anticoagulante natural que demuestra afinidad selectiva por estos autoanticuerpos, que al unírsele, induce trombosis por neutralizar su efecto anticoagulante. Son los autoanticuerpos mejor caracterizados en el síndrome al igual que aquellos dirigidos contra la protombina. En presencia de la anticardiolipina, se aumenta la captación de la LDL oxidada que es vital para el proceso atero-trombótico. Los AAF disminuyen las concentraciones de la anexina V, (proteína I anticoagulante placentaria), favoreciendo así los eventos trombóticos; esta proteína actúa como tromboreguladora y al ser desplazada por los autoanticuerpos se desencadena el proceso trombótico lo que se traduce en una insuficiencia placentaria como resultado de la oclusión de vasos placentarios, infartos y vasculopatía de las arterias espirales. Al inicio del embarazo se altera el desarrollo del trofoblasto, siendo incapaz de establecer una efectiva circulación fetoplacentaria y en etapas tardías hay un daño de la vasculatura uteroplacentaria con porosidad en la membrana vasculo-sincitial que permite el ingreso de autoanticuerpos IgG (12).

También se ha propuesto la teoría del mimetismo molecular en relación a procesos infecciosos, la cual explicaría el porqué muchas infecciones suelen acompañarse por la elevación de AAF y en algunos de las cuales dicha elevación se acompaña de manifestaciones clínicas del SAF. Las infecciones cutáneas (18%), la infección por el virus de la inmunodeficiencia humana (VIH) (17%), las neumonías (14%), las infecciones por virus de la hepatitis C (VHC) (13%) y las infecciones urinarias (10%) constituyen las infecciones más comúnmente encontradas como factores desencadenantes del SAF (73).

CARACTERÍSTICAS CLÍNICAS

El SAF es una enfermedad autoinmune caracterizada por trombosis tanto venosa como arterial, la cual puede afectar a cualquier órgano y cualquier tamaño de vaso (pequeño, mediano o grande); así que, el abanico de características clínicas es extremadamente amplio. En 1999, en una reunión de expertos celebrada en Sapporo, Japón, se establecieron los primeros criterios de clasificación para el SAF que incluyen tanto criterios clínicos caracterizados por trombosis venosas y/o arteriales y morbilidad en el embarazo, acompañados de criterios de laboratorio caracterizados por la presencia de aCL y/o AL (9). Recientemente en Sydney, Australia se hicieron unas modificaciones a los criterios de Sapporo, fundamentalmente en el apartado de criterios de laboratorio (10).

El SAF se puede presentar asociado a otras enfermedades autoinmunes, principalmente el LES. Cuando el SAF no se asocia a ninguna otra patología, se le conoce como SAF "primario" (16). Cervera y cols (20) describieron una de las series más amplias publicadas hasta la fecha, donde se estudiaron las características clínicas e inmunológicas de una serie de 1000 pacientes europeos con el SAF (Euro-Phospholipid Project Group). De estos pacientes, el 53% presentaban un SAF primario, el 36% presentaban un SAF asociado a LES, el 5% asociado a una forma incompleta de lupus ("lupus-like disease"), un 2% asociado a artritis reumatoide, y cerca de un 1% asociado a esclerosis sistémica, dermatomiositis y a vasculitis sistémicas (20).

Las principales manifestaciones clínicas al inicio del SAF fueron la trombosis venosa profunda (TVP) en 31% de los pacientes, la trombocitopenia en un 22%, el *livedo reticularis* en un 20%, el ictus en un 13%, la tromboflebitis superficial en un 9%, el tromboembolismo pulmonar (TEP) en un 9%, las pérdidas fetales en un 8%, los accidentes isquémicos transitorios (AIT) en un 7%, la anemia hemolítica en un 6% , las úlceras cutáneas en un 4% y la epilepsia en un 4% de los pacientes. Otras manifestaciones menos frecuentes fueron el infarto agudo de miocardio (IAM), la amaurosis fugax y la gangrena digital entre otros.

Durante el seguimiento, dichos pacientes desarrollaron una serie de manifestaciones clínicas propias del SAF. Las manifestaciones más frecuentes fueron la TVP en un 39%, las artralgias en un 38%, la trombocitopenia en un 30%, el *livedo reticularis* en un 24%, la migraña en un 20%, el ictus en un 20%, el TEP en un 14%, el engrosamiento o la disfunción valvular cardiaca en un 12%, los AIT en un 11% y las úlceras cutáneas en un 5%. Dentro de las manifestaciones obstétricas destacaron las pérdidas fetales tempranas (<10 semanas) en un 35% de las pacientes, las pérdidas fetales tardías (>10 semanas) en un 17%, la prematuridad en un 10%, la preeclampsia en un 9% y la eclampsia en un 4%.

Con respecto a las características inmunológicas, los aCL fueron detectados en el 88% de los pacientes, un 43% fueron positivos solo para IgG, un 12% solo para IgM y en un 32% fueron positivos para ambos; el AL fue positivo en un 53% de los pacientes, (en un 12% sólo y en un 41% acompañado de los aCL). Los anticuerpos antinucleares (ANAs) fueron positivos en un 60% de los pacientes, los anticuerpos anti-dsDNA en un 29%, los anticuerpos anti-Ro en un 14%, los anti-La en un 6%, los anti RNP en un 6%, el factor reumatoide en un 8% y las crioglobulinas en un 4%. Cabe recordar que un 36% de los pacientes tenían un SAF asociado a LES (20). A continuación se describen las principales afecciones del SAF por órganos.

- *Sistema nervioso central*

Las manifestaciones clínicas del SAF asociadas con el sistema nervioso central (SNC) incluyen los episodios trombóticos arteriales, fenómenos psiquiátricos y una variedad de

fenómenos no trombóticos (126). El ictus es la manifestación más frecuente del SNC en los pacientes con SAF. Se han encontrado AAF hasta en un 7% de pacientes no seleccionados con ictus. Incluso se describe que uno de cada 5 ictus en personas jóvenes (<45 años) está asociado al SAF (142). Los eventos isquémicos cerebrales pueden aparecer en cualquier territorio vascular y la edad media de aparición de la isquemia cerebral asociada a AAF es varias décadas menor que la que de la población típica con isquemia cerebral. Una revisión sistemática reciente, mostró que el AL es un factor de riesgo por sí solo para el desarrollo de trombosis cerebrales (arteriales y venosas), tanto para el primer evento como para las recurrencias (142). Una forma menos frecuente de enfermedad trombótica cerebral asociada al SAF es la trombosis del seno venoso sagital. El síndrome de Sneddon se caracteriza por la presencia de isquemia cerebral (ictus o AIT) acompañado de *livedo reticularis* difuso. Esta patología se caracteriza por una arteriopatía oclusiva no inflamatoria y afecta principalmente mujeres entre la cuarta y quinta décadas. Algunos autores han incluido al síndrome de Sneddon como una manifestación del SNC del SAF.

El SAF también se ha relacionado con el deterioro cognitivo, desde trastornos de memoria y concentración incipientes hasta la demencia. Recientemente, describimos una serie de 30 pacientes (21 mujeres y 9 hombres) con demencia asociada al SAF (63). La edad media en esta serie de pacientes fue de 49 años (rango 16 a 79 años). Diez pacientes tenían síndrome de Sneddon y 2 pacientes tenían lesiones cerebrales compatibles con enfermedad de Binswanger. Sólo un 37% de los pacientes tenían historia de ictus previos. El 63% de los pacientes tenían infartos corticales, el 30% infartos subcorticales y el 23% infartos en ganglios basales. A pesar de que un 63% de los pacientes tenían diagnostico de SAF antes del diagnóstico de la demencia, sólo un 37% de los pacientes recibían tratamiento anticoagulante. El tiempo medio entre el diagnóstico del SAF y el posterior desarrollo de la demencia fue de 3.5 años.

- *Piel*

Se ha comunicado una amplia variedad de manifestaciones cutáneas en pacientes con SAF, incluyendo el *livedo reticularis*, las úlceras cutáneas, la gangrena digital, la vasculitis necrotizante, los nódulos cutáneos, las máculas eritematosas, las hemorragias subungueales en astilla y la vasculitis livedoide. El *livedo reticularis* se caracteriza por un patrón reticular violáceo moteado con diferente localización, extensión, infiltración y regularidad del patrón reticular (20).

- *Corazón*

El SAF presenta diversas manifestaciones cardíacas. Las más importantes son la enfermedad valvular, la enfermedad arterial coronaria y menos frecuentes la miocardiopatía y los trombos intracardiácos. La enfermedad valvular aparece en alrededor del 48% de los pacientes con LES y con SAF primario (58). Se ha descrito una correlación positiva entre los niveles de AAF y la presencia de daño valvular. La mayoría de los casos son clínicamente asintomáticos y se detectan sólo por auscultación o por ecocardiografía. Alrededor del 5% de los pacientes progresan a una insuficiencia cardiaca y necesitan reemplazo valvular. Se pueden distinguir dos patrones ecocardiográficos morfológicos: masas valvulares (vegetaciones) y engrosamiento valvular (58). La anormalidad funcional predominante es la insuficiencia, mientras que la estenosis es rara.

La prevalencia de aCL en pacientes con IAM se sitúa entre un 5 y un 15%. El cribado rutinario para AAF en pacientes con IAM, es especialmente útil en pacientes menores de 45 años con antecedentes de trombosis venosas o arteriales (59). Adicionalmente, se ha encontrado una alta prevalencia de aCL en pacientes que son sometidos a cirugía de by-pass coronario y desarrollan oclusión tardía del injerto.

- *Riñón*

La afectación renal es una de las características del SAF, pudiendo afectar cualquiera de las estructuras vasculares renales las cuales conducen al desarrollo de hipertensión (HTA),

proteinuria, hematuria, síndrome nefrótico e insuficiencia renal. Inicialmente subestimado, es actualmente objeto de numerosos estudios. Los diferentes tipos de afectación renal en pacientes con SAF incluyen los siguientes: trombosis de capilares glomerulares, microangiopatía trombótica, necrosis cortical, nefropatía mesangial, trombosis o estenosis de la arteria renal y trombosis de la vena renal (64). La HTA es la manifestación clínica más frecuente, presente hasta en el 70% de los pacientes con SAF. Los mecanismos patogénicos que conducen a la HTA incluyen la trombosis del tronco de la arteria renal y las lesiones vasculares intrarenales. Algunos estudios han reportado una mayor pérdida del injerto en pacientes con LES sometidos a trasplante renal, como resultado de la trombosis post-trasplante.

-*Pulmón*

Las manifestaciones pulmonares del SAF incluyen el TEP y el infarto pulmonar, la hipertensión pulmonar tromboembólica, el síndrome de distrés respiratorio del adulto, la hemorragia alveolar y la trombosis microvascular. El embolismo pulmonar aparece en alrededor del 30% de los pacientes con SAF y aquellos casos de embolismo recurrente puede conducir a la hipertensión pulmonar tromboembólica (68). La prevalencia de la hipertensión pulmonar es alrededor del 3 al 5% en el SAF primario y del 2% en el SAF asociado al LES (20).

- *Manifestaciones hematológicas*

La manifestación hematológica más frecuente del SAF es la trombocitopenia. Aparece en el 25% de los pacientes y ocasionalmente es grave, oscilando el recuento de plaquetas entre 50 a 100 x 10^9 y el sangrado no es un problema frecuente. El papel exacto de los AAF en la trombocitopenia aún no está claro. Datos recientes sugieren la participación de anticuerpos dirigidos contra glucoproteínas específicas de membrana plaquetaria IIb/IIIa y Ib/IX. La anemia hemolítica puede estar presente en algunos pacientes con SAF y en ocasiones se asocia con la presencia de trombocitopenia, el denominado “síndrome de Evans” (20). Se ha

encontrado asociación entre la presencia de aCL de isotipo IgM con la anemia hemolítica autoinmune (20). Otras manifestaciones hematológicas más inusuales son la anemia hemolítica microangiopática (133), la coagulación intravascular diseminada (112) y la aplasia medular, fundamentalmente en la variante catastrófica del SAF.

- *Manifestaciones obstétricas*

El SAF se asocia a morbilidad y pérdidas tempranas y tardías durante el embarazo. Las pérdidas del embarazo pueden ser en forma de abortos, de muerte intrauterina, de muerte intraparto o de muerte neonatal. Con respecto a las pérdidas fetales, estas pueden ocurrir en cualquier momento durante el embarazo pero alrededor del 50% de los casos se presentan en el segundo y tercer trimestre de la gestación (131). Este es un dato que diferencia los abortos de este síndrome de los de la población general, que suelen ocurrir durante el primer trimestre del embarazo y suelen estar relacionados con causas no inmunológicas (alteraciones morfológicas o cromosómicas). La tasa de abortos en el SAF está aún por determinar aunque se llevan a cabo estudios epidemiológicos y la determinación de los AAF es ya prácticamente una prueba de rutina en mujeres con abortos recurrentes. En mujeres con historia de gestaciones normales, sólo un 2% tienen AL o aCL a cualquier título y menos de un 0,2% tienen títulos altos de estos anticuerpos. De aquí que la determinación de estos anticuerpos en mujeres embarazadas sin antecedentes obstétricos patológicos sea de poco valor. La historia de los embarazos previos es importante para determinar la validez de una prueba positiva para AAF. Se estima que si una paciente con LES tiene AL o al menos títulos medios del isotipo IgG de los aCL, el riesgo de aborto espontáneo en el primer embarazo es del 30%, y si tiene una historia de al menos 2 pérdidas fetales previas, el riesgo aumenta hasta el 70% en el siguiente embarazo.

Los mecanismos patogénicos que causan los abortos no se conocen completamente. Una trombosis progresiva de la microcirculación de la placenta condicionaría una insuficiencia placentaria, retardo en el crecimiento fetal y, finalmente, pérdida fetal (13). Esta podría ser una posible explicación, pero no en todas las placentas examinadas se han encontrado áreas de

infartos por lo que deben de existir además otros mecanismos. El feto abortado es generalmente normal exceptuando el retraso en el crecimiento. Parece, por tanto, que las alteraciones en la placenta son las responsables de las muertes intrauterinas. Las mujeres con AAF pueden presentar otras complicaciones como preeclampsia, insuficiencia utero-placentaria, partos prematuros y síndrome de HELLP (hemólisis, enzimas hepáticas elevadas y recuento de plaquetas bajo) (13).

SAF CATASTRÓFICO

Un reducido número de pacientes con SAF (1%) presentan una forma acelerada de trombosis de predominio en la microvasculatura, la cual conduce a fracaso multiorgánico y la muerte en un considerable número de casos. Dicha variante es conocida como SAF catastrófico (111). Debido a su rareza, se creó un registro internacional ("CAPS Registry") donde se recogen todos los casos descritos (tanto casos publicados como casos no publicados) del SAF catastrófico, lo cual ha permitido describir las características clínicas y el pronóstico de dichos pacientes, como también las diferentes pautas de tratamiento (106-107). El SAF catastrófico, difiere de la forma "clásica" de SAF en diferentes aspectos. El SAF clásico suele producir trombosis en un sólo vaso (arterial o venoso) de mediano o gran calibre y con tasas de recurrencias bajas con tratamiento anticoagulante. Por su parte el SAF catastrófico afecta a múltiples órganos a la vez con predominio de afectación parenquimal y de pequeños vasos. Alrededor de un 50% de los casos, se reconoce un factor desencadenante, principalmente infecciones, cirugías, suspensión de la anticoagulación, procesos neoplásicos, el embarazo y el puerperio entre otros (110).

Debido a la heterogeneidad de las formas de presentación del SAF catastrófico, se establecieron unos criterios preliminares de clasificación tras una reunión de expertos celebrada en Taormina, Italia en 2002 (108). Posteriormente, analizamos la validez de dichos criterios en 176 pacientes con SAF catastrófico (109). De acuerdo con estos criterios cerca del 51% de los pacientes tenían un SAF catastrófico definitivo, mientras que el 40% de los

pacientes tenían un SAF catastrófico probable, obteniendo una sensibilidad del 90% y una especificidad del 99%; por lo cual concluimos que los criterios de clasificación establecidos para el SAF catastrófico eran una herramienta útil para su estudio.

Las manifestaciones del SAF catastrófico dependen de 2 factores: los órganos afectados y la extensión de la trombosis, y las manifestaciones secundarias a la respuesta inflamatoria sistémica en relación a la liberación de citocinas de los tejidos necróticos. A diferencia de la forma "clásica" del SAF, el SAF catastrófico afecta órganos inusuales como testículos, ovarios y útero. Los pacientes tienen muy frecuentemente afectación pulmonar en forma de distrés respiratorio del adulto o hemorragia alveolar y afectación intraabdominal en forma de isquemia intestinal, insuficiencia suprarenal, microangiopatía trombótica renal, necrosis de la vesícula biliar ó infartos esplénicos entre otros (11). A diferencia también de la forma "clásica", el SAF catastrófico puede presentar formas más graves de trombocitopenia y hasta una quinta parte de los pacientes desarrollan una coagulación intravascular diseminada (112).

Las recurrencias o recaídas del SAF catastrófico son inusuales, ocurriendo en menos de 10 pacientes hasta la fecha. Al igual que en el primer evento, la prevención de los posibles factores desencadenantes es esencial para evitar nuevos episodios trombóticos (115).

A pesar de un tratamiento intensivo, la mortalidad del SAF catastrófico continua siendo alta (cerca del 50%). La combinación de anticoagulación más corticoesteroides y recambio plasmático parece ser la estrategia más eficaz en dichos pacientes. La terapia con inmunoglobulinas endovenosas también parece ser útil. Otras medidas de soporte en el paciente crítico como la ventilación mécanica, la hemofiltración continua y el uso de inotrópicos también son necesarias en muchos de estos pacientes. Las principales causas de muerte en estos pacientes la constituyen el compromiso del SNC (ictus, hemorragia cerebral y encefalopatía), el compromiso cardiaco y las infecciones (113).

HIPÓTESIS

El SAF es un síndrome protrombótico adquirido caracterizado por trombosis venosas y arteriales y pérdidas fetales recurrentes. Puede estar presente como SAF "primario" cuando no esta asociado a ninguna enfermedad autoinmune (fundamentalmente el LES) o en asociación a otros procesos tales como infecciones (principalmente infecciones virales crónicas) y procesos neoplásicos, entre otros. También puede manifestarse de una forma acelerada en días o semanas, caracterizado por trombosis de pequeños órganos y fallo multiorgánico, lo que se conoce como SAF "catastrófico".

A pesar de que hace más de 20 años se describió originalmente este síndrome, existen aún algunos aspectos no bien definidos. Nuestra hipótesis es que el SAF es una entidad con un amplio espectro de manifestaciones clínicas, incluyendo entre otras una variedad "primaria" que ocasionalmente evoluciona a un LES, una variedad asociada a procesos neoplásicos (tanto tumores sólidos como neoplasias hematológicas) y una variedad conocida como "catastrófica" la cual puede aparecer durante el embarazo o el puerperio.

OBJETIVOS

1. Objetivos del primer estudio

Long-term follow-up in 128 patients with primary antiphospholipid syndrome Do They Develop Lupus?. Medicine (Baltimore) 2005;84:225–230

Analizar las características clínicas y serológicas al inicio y durante el seguimiento en una amplia cohorte de pacientes con SAF primario y observar si tras un periodo de tiempo prolongado, dichos pacientes desarrollan otra enfermedad autoinmune como LES.

2. Objetivo del segundo estudio

Antiphospholipid antibodies associated with malignancies: Clinical and pathological characteristics of 120 patients. Semin Arthritis Rheum 2006; 35:322-32

Describir las características clínicas e inmunológicas de los pacientes con procesos neoplásicos y AAF, con especial énfasis en sus manifestaciones trombóticas, su pronóstico y su tratamiento.

3. Objetivo del tercer estudio

Catastrophic antiphospholipid syndrome during pregnancy and puerperium: maternal and fetal characteristics of 15 cases. Ann Rheum Dis 2007; 66:740-46

Evaluar las características clínicas y serológicas de una serie de pacientes con SAF catastrófico desencadenados durante el embarazo o el puerperio, con especial interés en el pronóstico materno y fetal.

PACIENTES Y MÉTODOS

1. Primer estudio

La cohorte inicial la constituyeron 201 pacientes de 4 hospitales universitarios de tercer nivel del Reino Unido, México y España los cuales fueron diagnosticados de SAF primario en 1987 (103 de la Unidad de Lupus del Hospital St Thomas de Londres, 50 de la Unidad de Reumatología del Instituto Nacional de Cardiología, Ignacio Chávez, en México DF, México; 30 del Hospital Regional Universitario Carlos Haya de Málaga y 18 del Hospital Reina Sofía de Córdoba, España). Setenta y tres pacientes no fueron incluidos en el análisis final debido a pérdidas en el seguimiento, por haber sido visitados solo en 1 ocasión (visitados para una segunda opinión) (n = 64) o porque no cumplieron los criterios clasificatorios de Sapporo (n = 9).

Finalmente, se incluyeron 128 pacientes con SAF primario (55 de Londres, 35 de México, 22 de Málaga y 16 de Córdoba). Dichos pacientes fueron seguidos en los diferentes centros de referencia durante Enero de 1987 a Julio de 2001.

Para evitar incluir pacientes con SAF asociado a una enfermedad autoinmune, se utilizaron los criterios de SAF primario de Piette y cols (18).

Los diferentes autoanticuerpos fueron determinados en cada uno de los centros incluyendo los ANAs, dsDNA, ENA, aCL y AL.

2. Segundo estudio

Se incluyeron 17 casos del "CAPS Registry" incluidos hasta Diciembre de 2003. El "CAPS Registry" es un registro internacional creado por el Forum Europeo para el estudio de los Anticuerpos Antifosfolipídicos.

Los restantes 103 casos fueron identificados mediante una búsqueda de la literatura mediante MEDLINE (National Library of Medicine, Bethesda, MD).

Se incluyeron todos los casos de neoplasias con AAF publicados en inglés, español, francés, alemán e italiano. Desde 1966 a 1983, se incluyeron aquellos casos con neoplasias y falsa positividad para VDRL o AL. Desde 1983 (cuando se describió el SAF) se incluyeron los aCL. Desde 1990 hasta Noviembre de 2003, se incluyeron también aquellos pacientes con anticuerpos anti β_2GPI. La información obtenida se resumió en un protocolo previamente establecido, donde se incluyó el género, la edad, el diagnóstico de base, el tipo de neoplasia, las principales manifestaciones trombóticas y serológicas, el tratamiento y el pronóstico.

3. Tercer estudio

Se revisaron los 255 casos que fueron incluidos en el "CAPS Registry" hasta el 1 de Noviembre de 2005. Se incluyeron sólo aquellos pacientes que cumplieron criterios para SAF catastrófico (109). Los casos fueron recolectados utilizando un formato pre-establecido donde se incluyó la edad, el género, el diagnóstico de base, el momento de presentación del SAF catastrófico (durante el embarazo o el puerperio), las manifestaciones clínicas y serológicas, el tratamiento y el pronóstico materno y fetal. La lista de los diferentes factores desencadenantes en el "CAPS Registry" fue utilizado como guía para identificación de los casos. El diagnóstico y la gravedad del síndrome de HELLP se realizó de acuerdo a los criterios internacionales previamente establecidos por Sibai y Martin respectivamente (132 y 133).

RESUMEN DE RESULTADOS

1. Primer estudio

En este estudio describimos una de las series más amplia y con más largo seguimiento de pacientes con SAF primario de 4 diferentes centros. La muestra final fue de 128 pacientes (97 mujeres y 31 hombres).

- La edad media fue de 42 años (rango, 16-79 años).
- El seguimiento medio fue de 9 años (rango, 2–15 años).
- Las principales manifestaciones al inicio fueron la TVP (33%), las pérdidas fetales (23%) y el ictus (13%).
- Durante el seguimiento, 62 (48%) pacientes tuvieron episodios de TVP y 19 tuvieron episodios recurrentes de TVP en 2 o más ocasiones.
- Las trombosis arteriales fueron más frecuentes, ocurriendo en 63 (49%) pacientes, incluyendo los ictus en 33 (26%) y los AIT en 29 (23%) pacientes.
- A 51 pacientes se les realizó una RM cerebral basal, siendo anormal en alrededor del 70% de los pacientes (principalmente se encontraron lesiones de isquemia).
- Se realizó ecocardiografía transtorácica basal en 93 pacientes. Los principales hallazgos patológicos fueron la enfermedad valvular mitral y aórtica en 18 (19%) y 7 (8%) pacientes respectivamente.
- De los 320 embarazos en nuestra cohorte de 97 mujeres, 177 (55%) terminaron con pérdidas fetales, 7 (4%) fueron prematuros y en 3 (1%) de los casos se diagnosticó preeclampsia.
- Durante el seguimiento, 9 de las 97 mujeres tuvieron 24 nuevos embarazos exitosos, mientras que 7 pacientes tuvieron 10 nuevas pérdidas fetales.
- Los principales hallazgos serológicos fueron la positividad para los aCL isotipo IgG en 110 (86) pacientes, seguido de los aCL isotipo IgM en 36 (39%), el AL en 71 (65%), los

ANAs en 47 (%) y el test de Coombs en 5 (4%) pacientes. Solo 3 pacientes desarrollaron anticuerpos anti dsDNA durante el seguimiento.

- En 8 (38%) de los 21 pacientes a los que se les realizó una nueva RM cerebral se les encontraron nuevos hallazgos patológicos.
- En 6 (22%) de los 27 pacientes que se les realizó una nueva ecocardiografía, se les encontraron nuevos hallazgos patológicos.
- Después de una duración media de la enfermedad de 8 años (rango 1 a 14), 110 (86%) pacientes continúan con el diagnóstico de SAF primario, 11 (8%) pacientes desarrollaron un LES, 6 (5%) una forma incompleta de lupus ("lupus-like disease") y 1 (1%) paciente desarrolló una miastenia gravis.
- Después de realizar un análisis estadístico mediante regresión logística, se encontró que únicamente la presencia del test de Coombs positivo confiere un riesgo estadísticamente significativo para el desarrollo de LES (OR, 66.4; 95% CI, 1.6–2714; p = 0.027).
- Al final del estudio, 113 (88%) de los pacientes continúan vivos, mientras que 15 (12%) pacientes fallecieron .

2. Segundo estudio

Se incluyeron un total de 120 casos con AAF asociados a procesos neoplásicos (62 hombres y 58 mujeres).

- La edad media fue de 56 años (rango entre 5 y 88 años).
- Las principales neoplasias hematológicas fueron el linfoma de células B en 10 (8%) pacientes, el linfoma esplénico en 8 (7%) y la leucemia mieloide crónica en 7 (6%) pacientes.
- Los principales tumores sólidos fueron el carcinoma de células renales en 7 (6%) pacientes, los tumores de primario desconocido en 7 (6%), el adenocarcinoma de pulmón en 6 (5%) y el cáncer de mama en 6 (5%) pacientes.

- En 41 pacientes se diagnosticaron simultáneamente ambas patologías (SAF y cáncer), en 29 casos, la neoplasia se diagnosticó después de las manifestaciones trombóticas del SAF y en 25 casos, las manifestaciones de SAF aparecieron después al diagnóstico de la neoplasia.
- Se encontraron manifestaciones trombóticas en 76 (71%) pacientes.
- Setenta y tres (21%) pacientes cumplieron criterios de Sapporo.
- Las principales manifestaciones del SAF fueron la trombocitopenia en 27 (25%) pacientes, el ictus en 25 (24%), la TVP en 20 (19%) y el TEP en 16 (15%) pacientes.
- El AL fue positivo en 70/104 (67%) pacientes, los aCL en 70/104 (67%) (52 isotipo IgG y 20 del isotipo IgM) los anti $ß_2$GPI en 6 (6%) y 4 (4%) pacientes tuvieron anemia hemolítica.
- Setenta y un pacientes (63%) se recuperaron o se mantienen vivos después del tratamiento de su neoplasia.
- La presencia de infartos pulmonares, el compromiso renal y suprarenal, la trombosis intestinal y la trombosis esplénica estuvieron relacionadas con un mal pronóstico.
- A pesar de que la información con respecto a la desaparición de los AAF después del tratamiento para la neoplasia no estuvo disponible en todos los casos, 23 (35%) de los 65 casos disponibles, negativizaron los AAF después del tratamiento de la neoplasia, especialmente aquellos pacientes con linfoma esplénico y los que fueron sometidos a nefrectomía.

3. Resultados tercer estudio

Se incluyeron 15 pacientes con SAF catastrófico que ocurrieron durante el embarazo o el puerperio (3 casos nuevos y 12 del “CAPS Regitry”).

- La edad media al momento del SAF catastrófico fue de 27 años (rango entre 17 y 38 años).

- La información sobre los antecedentes obstétricos fue disponible en 14 casos. Sólo una paciente tenía historia de embarazos exitosos, 9 pacientes habían tenido abortos previos o pérdidas fetales y 4 pacientes no tenían historia de embarazos previos.
- Siete (50%) de 14 casos ocurrieron durante el embarazo (entre la semana 17 y 38 de gestación), 6 (43%) ocurrieron en el puerperio (entre el segundo día y 3 semanas después del parto) y 1 (7%) paciente después de un curetaje por muerte fetal.
- En 4 (26%) pacientes, el SAF catastrófico fue la primera manifestación del SAF.
- Las características clínicas generales del SAF catastrófico durante el embarazo o el puerperio fueron similares a las del SAF catastrófico desencadenado por otros factores a excepción de una tasa mayor de abortos previos.
- Las principales manifestaciones clínicas fueron el compromiso renal en 11 (73%) pacientes, el compromiso pulmonar en 11 (73%), el compromiso del SNC en 9 (60%) y el síndrome de HELLP en 8 (53%) pacientes.
- Se encontró una serie de manifestaciones particulares en este grupo de pacientes, tales como los infartos placentarios en 4 (27%) pacientes, la trombosis de la vena pélvica en 1 (7%) paciente y la microangiopatía trombótica del miometrio en 1 (7%) paciente.
- Catorce (93%) pacientes fueron positivos para los aCL, 12 (80%) para el isotipo IgG y 4 (27%) para el isotipo IgM. El AL fue positivo en 10 (73%) pacientes y los anti $ß_2$GPI en 3 (20%) pacientes.
- Siete (46%) madres murieron como consecuencia del SAF catastrófico. El pronóstico fetal fue disponible en 13 casos. Únicamente 6 (46%) neonatos sobrevivieron (3 de ellos fueron neonatos prematuros), mientras que 7 (54%) fallecieron. No se encontraron diferencias en el pronóstico de las madres o de los bebés con respecto a los antecedentes de síndrome de HELLP o el tratamiento que recibieron incluyendo la terapia combinada con anticoagulación y recambios plasmáticos.

CONCLUSIONES

1. Conclusiones del primer trabajo

- Al igual que el SAF asociado al LES, las principales manifestaciones del SAF primario son las pérdidas fetales, las trombosis arteriales y venosas.
- Alrededor de dos tercios de los pacientes con SAF primario presentan alteraciones en la RM cerebral. A pesar del tratamiento anticoagulante, pueden aparecer nuevas lesiones en la RM (principalmente isquémicas) durante el seguimiento.
- Un tercio de los pacientes presentan alteraciones cardiacas en la ecocardiografía basal (principalmente lesiones valvulares). Al igual que ocurre en el SNC, nuevas lesiones pueden aparecer en el seguimiento a pesar de la terapia anticoagulante.
- Después de un período de seguimiento largo, alrededor de un 10% de los pacientes con SAF primario fallecen, principalmente por TEP y eventos cardiovasculares.
- Nuestro estudio confirma que es inusual que un SAF primario evolucione hacia un LES o una forma incompleta de lupus, incluso tras un período largo de seguimiento. El test de Coombs positivo puede ser un marcador para el posterior desarrollo de LES en dichos pacientes.

2. Conclusiones del segundo trabajo

- Los AAF pueden estar relacionados a una serie de procesos neoplásicos incluyendo tumores sólidos (principalmente el carcinoma de células renales, el adenocarcinoma de pulmón y el cáncer de mama) y neoplasias hematológicas (linfoma de células B, linfoma esplénico y la leucemia mieloide crónica, entre otros).
- Una vez el proceso neoplásico esta en remisión, los AAF pueden desaparecer hasta en una tercera parte de los pacientes. Esta característica particular no suele observarse en otros escenarios del SAF asociado a enfermedades autoinmunes o procesos infecciosos.

- Basados en nuestro estudio, es importante considerar, especialmente en personas mayores, que los eventos tromboembólicos asociados al SAF pueden ser la primera manifestación de una neoplasia oculta. A su vez, la presencia de los AAF puede tener connotaciones importantes en el tratamiento de los pacientes con procesos neoplásicos.

3. Conclusiones del tercer trabajo

- El embarazo y el puerperio son periodos transitorios de hipercoagulabilidad que predisponen al desarrollo de trombosis, especialmente en aquellos pacientes con una susceptibilidad de base, como los pacientes con SAF.
- El SAF está relacionado con una serie de complicaciones obstétricas que incluyen las pérdidas fetales recurrentes, la preeclampsia, el retardo en el crecimiento intrauterino, la insuficiencia fetoplacentaria y el parto prematuro.
- En alrededor de un 6% de los casos, el SAF catastrófico puede presentarse durante el embarazo o el puerperio.
- Las pacientes con SAF catastrófico durante el embarazo o el puerperio presentan una serie de características particulares, como el síndrome de HELLP, la trombosis placentaria, la microangiopatía trombótica de miometrio o la trombosis de la vena pélvica.
- La mortalidad materna y fetal del SAF catastrófico durante el embarazo o el puerperio es muy alta (46 y 54% respectivamente).
- Basados en nuestros datos, consideramos importante considerar la posibilidad de desarrollar un SAF catastrófico en aquellos pacientes con signos de síndrome de HELLP y fracaso multiorgánico durante el embarazo o el puerperio, especialmente en las pacientes con historia de trombosis y/o pérdidas fetales.

4. Conclusión final

El SAF primario es una entidad propia ampliamente reconocida que en raras ocasiones evoluciona a un LES, incluso tras un período largo de seguimiento. El SAF puede asociarse a una serie de procesos crónicos como lo son las neoplasias hematológicas y los tumores sólidos. En aquellos casos con la variante "catastrófica" del SAF, el embarazo y el puerperio, constituyen un período de alta susceptibilidad para el desarrollo de esta variante altamente letal del SAF.

APPENDIX II: Related published papers

Veinte años del síndrome antifosfolipídico: pasado, presente y futuro

Twenty years of the antiphospholipidic syndrome: past, present and future

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Introducción

Hace casi cien años que se describieron las primeras pruebas reagínicas como técnicas de detección de infecciones treponémicas, las cuales se fueron perfeccionando a lo largo del siglo pasado y permitieron reconocer a algunos pacientes que presentaban falsa positividad de dichas pruebas y desarrollaban enfermedades autoinmunes y trombosis. Así mismo, en los años cincuenta del pasado siglo se describió el fenómeno "anticoagulante lúpico", y se observó que se asociaba en muchas ocasiones a la presencia de serología luética falsamente positiva. Pero no fue hasta hace sólo 20 años, que el doctor Graham Hughes describe por primera vez la asociación de manifestaciones trombóticas, abortos, enfermedad neurológica y la presencia de anticoagulante lúpico como constitutivos de un síndrome no descrito previamente como tal (1). Desde entonces, las investigaciones llevadas a cabo por el equipo del doctor Hughes en los hospitales londinenses de Hammersmith y, posteriormente, de St Thomas han permitido que el síndrome antifosfolipídico (SAF) haya ganado un sitio muy importante entre las enfermedades autoinmunes alrededor de todo el mundo (2, 3).

La identificación de pacientes que padecían trombosis acompañadas de anticuerpos antifosfolipídicos (AAF) sin la presencia de manifestaciones características del lupus eritematoso sistémico (LES) o la presencia de anticuerpos antinucleares llevó a la descripción cinco años después del SAF primario (4), el cual con el paso de los años ha adquirido su propia "personalidad" pasando de ser la "hermana menor" del LES a una entidad con características propias y cada vez más identificada en la práctica clínica. El seguimiento a largo plazo de estos pacientes con SAF primario ha permitido definir que estos pacientes raras veces evolucionan a un LES u otra enfermedad autoinmune y permanecen como SAF primario a pesar del paso de los años (5).

El papel de los AAF no sólo se ha quedado en su participación en accidentes trombóticos de la macrocirculación como claro factor de riesgo independiente en la enfermedad cerebrovascular, el infarto agudo de miocardio o la trombosis venosa profunda, entre otros, sino que también participa en otros múltiples procesos trombóticos tales como en la reestenosis de endoprótesis vasculares, trombosis postrasplante de órganos sólidos, tales como riñón (6) o hígado (7) y más recientemente, se ha asociado también la presencia de dichos anticuerpos a una incidencia mayor de fallos en la fertilización embrionaria *in vitro* e infertilidad (8). Precisamente, el SAF se ha convertido en un tema de suma importancia en el ámbito obstétrico, no en vano actualmente es la principal causa tratable de pérdidas fetales recurrentes. Los AAF intervienen durantes todas las fases de la gestación, produciendo alteraciones en la implantación placentaria, además de conferir un riesgo sustancialmente importante para el desarrollo de preeclampsia, insuficiencia uteroplacentaria y prematuridad. Un buen consejo prenatal, un seguimiento ecográfico y clínico y un tratamiento antiagregante o anticoagulante, si es el caso, son mandatorios para tener un embarazo exitoso en estos pacientes (9).

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Anticuerpos antifosfolipídicos: trombosis y ateroesclerosis

El paso de los años no sólo nos ha permitido conocer las características clínicas de este síndrome sino que también nos ha enseñado sobre su patogénesis. Los modelos animales, tanto espontáneos como experimentales, desarrollados por Shoenfeld et al (10) nos han permitido entender la patogenicidad de sus características *in vitro* y su fisiopatogenia y nos ha permitido vislumbrar nuevas estrategias terapéuticas.

Merece especial comentario la creciente asociación entre los procesos autoinmunes como el SAF y la ateroescelerosis. Los AAF no solamente tienen unas propiedades procoagulantes, sino también proaterogénicas, demostradas mediante modelos animales y ensayos clínicos en los que se ha evidenciado un incremento de accidentes cardiovasculares en los pacientes con AAF (11).

Las manifestaciones trombóticas del SAF en algunas ocasiones se presentan en una forma dramática y devastadora y es lo que se conoce como el SAF catastrófico (12), caracterizado por la presencia de microtrombosis en tres o más órganos en un corto período, lo cual lleva a una alteración multiorgánica y, en casi la mitad de los casos, a la muerte. Los más de 200 casos reunidos hasta el momento (CAPS registry http://www.med.ub.es/MIMMUN/FORUM/REGISTRY1.HTM), nos permiten afirmar que si bien la mortalidad continúa elevada, solamente una alta sospecha clínica, un rápido y agresivo tratamiento inmunodepresor, anticoagulación y recambio plasmático y/o inmunoglobulinas endovenosas, nos permite apagar y aminorar los síntomas de esta "tormenta" trombótica.

Congresos y grupos de investigación

La complejidad y heterogeneidad del SAF ha permitido desarrollar grupos interdisciplinarios compuestos por internistas, reumatólogos, hematólogos, ginecoobstetras e inmunólogos, entre otros, que han permitido entender y avanzar rápidamente en el tema. Se han realizado hasta la fecha diez congresos internacionales bianuales de expertos en la materia, comenzando en el año 1984 en Londres y, posteriormente, Kingston, Sirmione, San Antonio, Leuven, New Orleans, Sapporo, Tours y recientemente Taormina, las cuales han permitido definir y unificar múltiples conceptos del SAF, como la estandarización del laboratorio, el desarrollo de criterios de clasificación y la conformación de grupos de trabajo internacionales. Fruto de esos grupos de trabajo son las descripciones multicéntricas de grandes series de pacientes (13), las cuales nos han permitido conocer mejor y de una manera detallada las múltiples características clínicas, serológicas, terapéuticas y pronósticas de los pacientes con SAF.

¿Qué nos deparará el futuro?

Veinte años después, tanto el doctor Hughes como muchos expertos en el tema hipotetizan sobre la participación de los AAF en muchas otras situaciones clínicas muy prevalentes, tales como la migraña, la pérdida de la memoria o la enfermedad de Alzheimer, entre otras. Igualmente, quedan aún muchos interrogantes por responder acerca de la patogénesis, la profilaxis y el tratamiento. ¿Qué hacer ante un paciente asintomático y con concentraciones persistentemente elevadas de AAF? ¿Es suficiente la antiagregación plaquetaria? ¿Se debe anticoagular manteniendo INR bajos? ¿Qué tratamiento se debe instaurar en pacientes que presentan trombosis a pesar de la anticoagulación y antiagregación con aspirina? ¿Qué hacer con las mujeres embarazadas que continúan presentando abortos a pesar del tratamiento con heparina y aspirina? Estas y quizá muchas otras preguntas quedan por responder. La utilización de otros tratamientos tales como las inmunoglobulinas endovenosas, los nuevos antiagregantes y anticoagulantes y, lo que es más importante, el desarrollo de ensayos clínicos aleatorizados (algunos ya en marcha) nos permitirá conocer y entender cuál es el tratamiento ideal de este cada vez más añejo y adulto síndrome.

Referencias

1. **Hughes GRV.** Thrombosis, abortion, cerebral disease and the lupus anticoagulant. *Br Med J* 1983;**287**:1088-1089.
2. **Asherson RA, Cervera R, Piette JC, Shoenfeld Y.** Milestones in the antiphospholipid syndrome. The antiphospholipid syndrome II:Autoimmune thrombosis. *Elsevier* 2002:3-5.
3. **Khamashta M.** Hughes syndrome:History. Hughes syndrome. Antiphospholipid syndrome. London: Springer-Verlag 2000;**1**:3-7.
4. **Asherson RA, Khamashta MA, Ordi-Ros J, et al.** The "primary" antiphospholipid syndrome: major clinical and serological features. *Medicine* (Baltimore) 1989;**68**:366-74.
5. **Gómez-Puerta JA, Martín H, Amigo MC, et al.** Long-term follow-up in 128 patients with Primary Antiphosphoplipid Syndrome (PAPS). Do they develop Lupus? *Arthritis Rheum* 2001;**44**: S146.
6. **Stone JH, Amend WJ, Criswell LA.** Antiphospholipid antibody syndrome in renal transplantation: occurrence of clinical events in 96 consecutive patients with systemic lupus erythematosus. *Am J Kidney Dis* 1999;**34**:1040-7.
7. **Villamil A, Sorkin E, Basta MC, et al.** Catastrophic antiphospholipid syndrome complicating orthotopic liver transplantation. *Lupus* 2003;**12**:140-3.
8. **Balasch J, Cervera R.** Reflections on the management of reproductive failure in the antiphospholipid syndrome-the clinician's perspective. *Lupus* 2002;**11**:467-77.
9. **Shehata HA, Nelson-Piercy C, Khamashta MA.** Management of pregnancy in antiphospholipid syndrome. *Rheum Dis Clin North Am* 2001;**27**:643-59.
10. **Sherer Y, Shoenfeld Y.** Antiphospholipid syndrome: insights from animal models. *Curr Opin Hematol* 2000;**7**:321-4.
11. **George J, Haratz D, Shoenfeld Y.** Accelerated atheroma, antiphospholipid antibodies, and the antiphospholipid syndrome. *Rheum Dis Clin North Am* 2001; **27:**603-10.
12. **Asherson RA, Cervera R, Piette JC, et al.** Catastrophic antiphospholipid syndrome: clues to the pathogenesis from a series of 80 patients. *Medicine* (Baltimore) 2001;**80**:355-77.
13. **Cervera R, Piette JC, Font J, Khamashta MA, Shoenfeld Y, Camps MT, et al.** Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. *Arthritis Rheum* 2002; **46**:1019-27.

Letter to the Editor

"Catastrophic" Antiphospholipid Syndrome

***To the Editor*:** "Catastrophic" antiphospholipid syndrome (CAPS), an unusual but often fatal complication of the antiphospholipid syndrome (APS), is characterized by multiorgan failure due to microvascular thrombosis in 3 or more organs.[1] The article by Dy and Swaroop[2] described a 31-year-old woman with a history of systemic lupus erythematosus (SLE) who had an acute episode of renal failure accompanied by frank proteinuria (9 g/24 h), hypertension, and renal biopsy–proven active grade 4 glomerulonephritis. Three weeks later, the patient presented with confusion and behavior changes. She had no signs of meningoencephalitis on cerebrospinal fluid examination, but vasogenic edema with white matter involvement was evident on magnetic resonance imaging. She had deep venous thrombosis in the left popliteal vein, Coombs-negative hemolytic anemia with schistocytes in the peripheral smear, thrombocytopenia, prolonged activated partial thromboplastin time, and factor XII deficiency. Lupus anticoagulant activity was absent, and the anticardiolipin antibody status was not reported.

This case of a patient with SLE with multiorgan involvement (neurologic, hematologic, and renal), deep venous thrombosis of the lower extremity, and markers of microangiopathic involvement (schistocytes) suggests an episode of CAPS. Antiphospholipid syndrome without antiphospholipid antibodies at the time of the thrombotic event has been described previously.[3] Futhermore, autoantibodies against factor XII have been reported recently in patients with APS.[4]

***Report of a Case.*—**We recently encountered a similar situation in a 37-year-old woman with a 7-year history of SLE characterized by episodes of cutaneous involvement (malar rash, photosensitivity, Raynaud phenomenon, and diffuse alopecia), pericarditis, autoimmune hemolytic anemia, and grade 2 glomerulonephritis at diagnosis that evolved 5 years later to grade 3 disease. The patient's serologic profile included antinuclear and anti–double-stranded DNA (anti-dsDNA) antibodies in high titers as well as the presence of anti-Ro (anti–SS-A), anti-La (anti–SS-B), anti-ribonucleoprotein, and Smith (anti-Sm) antibodies. A 2-year course of intravenous cyclophosphamide yielded a poor response. Additionally, the patient had APS and a history of 2 fetal losses, subungual splinter hemorrhages, livedo reticularis, and high titers of IgG and IgM anticardiolipin antibodies on several determinations.

The patient was taking aspirin (125 mg/d), prednisone (20 mg/d), and chloroquine (150 mg/d) before she was hospitalized for treatment of nephrotic syndrome characterized by peripheral edema, a low serum albumin level, and proteinuria (6.2 g/24 h). During hospitalization, her renal function deteriorated, and hypertension and hematuria developed. A renal biopsy disclosed grade 4 glomerulonephritis with glomerular microthrombosis. Pulse therapy with methylprednisolone and cyclophosphamide was initiated, and anticoagulants were administered. One week later, the patient had sudden development of hemoptysis, dyspnea, and hypoxemia, and chest radiography revealed diffuse bilateral alveolar infiltrates. She was transferred to the intensive care unit and placed on mechanical ventilation and continuous hemofiltration therapy. With a clinical diagnosis of probable CAPS, plasma exchange was initiated. At that time, laboratory tests disclosed high levels of anti-dsDNA antibodies and D-dimer products, low complement levels, severe anemia, and the presence of schistocytes. Antiphospholipid antibodies, including IgG and IgM anticardiolipin antibodies and lupus coagulant, were absent. A week later, sepsis due to *Enterococcus faecalis* and a left subclavian thrombosis developed. The patient had an acute episode of pulmonary hypertension and died of multiorgan failure.

***Conclusion.*—**Recently, an international consensus meeting was held in Taormina, Italy, to clarify and establish international criteria for the diagnosis and treatment of CAPS.[5] According to these criteria, our patient would be classified as having definitive CAPS. Because we are not aware of the antiphospholipid antibody status of the patient described by Dy and Swaroop,[2] we would categorize their reported patient as having "probable" CAPS, a new category introduced in the Taormina criteria. These new criteria emphasize the need for antiphospholipid antibody screening in patients with multiorgan thrombotic failure.

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1. Asherson RA, Cervera R, Piette JC, et al. Catastrophic antiphospholipid syndrome: clues to the pathogenesis from a series of 80 patients. *Medicine (Baltimore)*. 2001;80:355-377.
2. Dy GK, Swaroop VS. 31-Year-old woman with confusion and labile behavior. *Mayo Clin Proc*. 2002;77:557-560.
3. Miret C, Cervera R, Reverter JC, et al. Antiphospholipid syndrome without antiphospholipid antibodies at the time of the thrombotic event: transient 'seronegative' antiphospholipid syndrome? *Clin Exp Rheumatol*. 1997;15:541-544.
4. Jones DW, Nicholls PJ, Donohoe S, Gallimore MJ, Winter M. Antibodies to factor XII are distinct from antibodies to prothrombin in patients with the anti-phospholipid syndrome. *Thromb Haemost*. 2002;87:426-430.
5. Asherson RA, Cervera R, de Groot PG, et al. Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines. *Lupus*. In press.

***In reply*:** We thank Drs Gómez-Puerta and colleagues for their insights into our case, a 31-year-old woman with active SLE who presented with global cognitive dysfunction, and their emphasis on the newly described entity of CAPS. We agree that the multiorgan involvement in our patient, most likely secondary to her underlying SLE, makes CAPS a diagnostic

probability. During the initial work-up, assays for antiphospholipid antibodies, in addition to the lupus anticoagulant, were negative. However, this point was not mentioned in our article because of space constraints. Inhibitors of factor XII were not detected; prolonged incubation of the patient's plasma with normal plasma showed no progressive decrease of factor XII activity over time.[1] Moreover, our patient's clinical presentation, as well as the diffusion-weighted magnetic resonance images and apparent diffusion coefficient maps, were consistent with vasogenic edema. In contrast, neurologic disorders associated with simple APS are primarily focal[2] as a result of parenchymal ischemia or infarction (unless rostral brainstem ischemia from rostral basilar artery thrombosis causes a "top-of-the-basilar syndrome"). In patients with simple APS, diffusion-weighted magnetic resonance images and apparent diffusion coefficient maps would reveal cytotoxic edema.[3] Nevertheless, we did recommend repeat determinations of antiphospholipid antibody levels in 6 months. Our patient remained well under the care of her primary physician, and no further evaluation was obtained.

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1. Feinstein DI. Inhibitors of blood coagulation. In: Hoffman R, Benz EJ Jr, Shattil SJ, et al, eds. *Hematology: Basic Principles and Practice*. 3rd ed. Philadelphia, Pa: Churchill-Livingstone; 2000:1970.
2. Levine SR, Brey RL. Neurological aspects of antiphospholipid antibody syndrome. *Lupus*. 1996;5:347-353.
3. Ay H, Buonanno FS, Rordorf G, et al. Normal diffusion-weighted MRI during stroke-like deficits. *Neurology*. 1999;52:1784-1792.

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EXTENDED REPORT

Antiphospholipid syndrome associated with infections: clinical and microbiological characteristics of 100 patients

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Objective: To describe and analyse the clinical characteristics of 100 patients with antiphospholipid syndrome (APS) associated with infections.
Methods: Patients were identified by a computer assisted search (Medline) of published reports to locate all cases of APS published in English, Spanish, and French from 1983 to 2003. The bilateral Fisher exact test was used for statistics.
Results: 59 female and 41 male patients were identified (mean (SD) age, 32 (18) years (range 1 to 78)): 68 had primary APS, 27 had systemic lupus erythematosus, two had ''lupus-like'' syndrome, two had inflammatory bowel disease, and one had rheumatoid arthritis. APS presented as a catastrophic syndrome in 40% of cases. The main clinical manifestations of APS included: pulmonary involvement (39%), skin involvement (36%), and renal involvement (35%; nine with renal thrombotic microangiopathy, RTMA). The main associated infections and agents included skin infection (18%), HIV (17%), pneumonia (14%), hepatitis C (13%), and urinary tract infection (10%). Anticoagulation was used in 74%, steroids in 53%, intravenous immunoglobulins in 20%, cyclophosphamide in 12%, plasma exchange in 12%, and dialysis in 9.6%. Twenty three patients died following infections and thrombotic episodes (16 with catastrophic APS). Patients given steroids had a better prognosis ($p = 0.024$). The presence of RTMA and requirement for dialysis carried a worse prognosis ($p = 0.001$ and $p = 0.035$, respectively).
Conclusions: Various different infections can be associated with thrombotic events in patients with APS, including the potentially lethal subset termed catastrophic APS. Aggressive treatment with anticoagulation, steroids, and appropriate antibiotic cover is necessary to improve the prognosis.

The detection of antiphospholipid antibodies (aPL)—that is, lupus anticoagulant or anticardiolipin antibodies—is of interest because of their importance in the pathogenesis of clotting in the antiphospholipid syndrome (APS). APS occurs not only in systemic autoimmune diseases, particularly systemic lupus erythematosus (SLE), but also in patients who do not manifest overt symptoms of other autoimmune disturbances (primary APS), where the emphasis is primarily on vascular events.[1 2]

Since 1983, many infections have been found to be associated with aPL positivity, although a pathogenic role for these antibodies was not usually obvious except in a few isolated cases. Over recent years it has been emphasised and reported on several occasions[3–5] that many infections may not only trigger the production of these antibodies but also appear be accompanied by clinical manifestations of the APS itself. This has been seen particularly in patients with catastrophic APS.[6–8]

In this study we made the first literature analysis—some 20 years after the definition of APS—of patients who developed an APS associated with, and probably triggered by, infections. In this series, comprising a total of 100 patients, we further clarify the importance of this association and discuss other clinical aspects, including treatment and prognosis.

METHODS

Patients were identified by a computer assisted search of published reports (Medline, National Library of Medicine, Bethesda, Maryland, USA) to locate all cases of APS published in English, Spanish, and French from 1983 (when APS was first defined) to 2003.

We also analysed several original cases that were categorised as having APS or as having aPL or lupus anticoagulant associated with any infection in which there was a thrombotic process. We scanned bibliographies of all articles for references not identified in the initial search. Only cases with well documented clinical summaries and relevant information were included in the review.

Data from these papers were summarised using a standardised data form, including sex, age, diagnosis of the underlying condition, associated infections, major thrombotic clinical manifestations, immunological features, treatment, and course. Two new cases of APS from our clinics, both associated with urinary infection, are added to the review as illustrative case reports (see the appendix).

The bilateral Fisher exact test was used for statistics.

RESULTS

In all, 100 patients with APS manifestations associated with infections were reviewed: 98 from the literature search[6–56] plus two from our own clinics.

General characteristics

General clinical features of these patients are shown in table 1. Fifty nine per cent were female and 41% male. Their mean (SD) age was 32 (18) years (range 1 to 78). There were 24 young patients (under 18 years), who were affected mainly by skin and respiratory infections. Sixty eight patients had primary APS, 27 had SLE, two had ''lupus-like'' disease, two had inflammatory bowel disease (one Crohn's disease

Abbreviations: aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; RTMA, renal thrombotic microangiopathy

Table 1 General characteristics

	Per cent (n = 100)
Female	59
Male	41
SLE	27
Primary APS	68
Catastrophic APS	40
Lupus-like	2
Rheumatoid arthritis	1
IBS	2

APS, antiphospholipid syndrome; IBS, inflammatory bowel disease.

and one ulcerative colitis), and one had rheumatoid arthritis. In 40 of the 100 cases, the thrombotic events appeared in the form of catastrophic APS.

Clinical presentation

Pulmonary involvement was present in 39 patients: in 24 as adult respiratory distress syndrome (ARDS), in 18 as pulmonary embolism, in three as pulmonary haemorrhage, and in one as pulmonary hypertension. Skin involvement was reported in 36 patients: 16 had livedo reticularis, nine had purpura fulminans, eight had skin ulcers, and three had digital necrosis. Renal involvement was reported in 35 patients, nine of whom had renal thrombotic microangiopathy (RTMA). Almost one third of the patients (31%) had cerebral disease, manifested as cerebrovascular accidents (CVA) in 21 patients, encephalopathy in seven, and other cerebral features in seven, including seizures, psychosis, or cerebral microinfarcts. Peripheral thrombosis was reported in 30 patients (15 had deep vein thrombosis). Other types of vascular thrombosis were: femoral artery occlusions in nine patients, vena cava thrombosis in four, radial artery thrombosis in one, and thrombosis of other arteries in three. Cardiac disease was found in 24 patients, presenting as myocardial infarction in 12, valve lesions in 10, and cardiac microthrombi in one; other cardiac features were reported in five (cardiogenic shock and atrial thrombus). Ten patients had avascular necrosis of the hip joint, in all cases accompanied by HIV infection. In only one case was the previous use of steroids reported (given for thrombocytopenia). We excluded all cases with other possible causes of avascular necrosis, including high triglyceride levels or protease inhibitor use. The remaining APS manifestation are summarised in table 2.

Associated infections

The associated infections and microbiological agents are shown in table 3. Skin infection (18%), human immunodeficiency virus (HIV) infection (17%), pneumonia (14%), hepatitis C virus (HCV) infection (13%), and urinary infection (10%) were the commonest associated infections. In nine cases, more than one organ or agent was identified as a source of infection. Other infections less frequently associated with APS were identified, including mycoplasma (3), cytomegalovirus (CMV) (3), fungal infections (2), pulmonary tuberculosis (2), malaria (2), *P carinii* (1), and leptospirosis (1).

Treatment

Most of the patients received the appropriate antibiotic and antiviral treatment according to the underlying infection. In five cases, this was given as sole treatment. The treatment was not reported in 17 cases. Table 4 shows the differing types of treatment used. Anticoagulation was the most common, used in 61 of 83 patients (73%). Steroids were used in 43 patients (53%), intravenous immunoglobulins in 17 (20%), cyclophosphamide in 10 (12%), and plasma exchange in 10 (12%). Aspirin was used in six patients (7%), dialysis in eight (10%), fibrinolytics in six (7%), and fresh frozen plasma in five (6%). Different types of surgical procedures were undertaken, including arthroplasty in three (4%), leg amputation in two (2%), and vena cava filter, aortic repair, or splenectomy in one case (1%) each.

Outcome

Twenty three patients died following infection and thrombotic episodes (in 16 cases with catastrophic APS). Other causes of death were related to RTMA (four cases), purpura fulminans (one case), CVA in a patient with varicella pneumonia, and HIV infection in one patient. Patients who received steroids had a better prognosis than the rest ($p = 0.024$). The presence of RTMA and need for dialysis carried a worse prognosis ($p = 0.001$ and $p = 0.035$, respectively). The remaining 77 patients recovered after the thrombotic event.

Table 2 Manifestations of antiphospholipid syndrome

	Per cent (n = 100)
Pulmonary	39
ARDS	24
Pulmonary embolism	18
Pulmonary haemorrhage	3
Pulmonary hypertension	1
Skin	36
Livedo reticularis	16
Purpura fulminans	9
Skin ulcers	8
Digital necrosis	3
Renal	35
RTMA	9
Cerebral	31
CVA	21
Encephalopathy	7
Other cerebral	7
Peripheral thrombosis	30
DVT	15
Femoral artery	9
Caval thrombosis	4
Radial artery	1
Other arteries	3
Cardiac	24
Myocardial infarction	12
Valve lesion	10
Cardiac microthrombi	1
Other cardiac	5
Intra-abdominal	
Hepatic	12
Splenic	8
Neuropathy	7
Intestinal	6
Mesenteric	5
Portal	4
Pancreas	3
Others	
Avascular necrosis	10
Genital	2
Amaurosis fugax	2
Other manifestations	6

ARDS, adult respiratory distress syndrome; CVA, cerebrovascular accident; DVT, deep vein thrombosis; RTMA, renal thrombotic microangiopathy.

Table 3 Associated infections

Agent or type	Per cent (n = 100)*
Skin	18
HIV	17
VZV	15
Pneumonia	14
HCV	13
Urinary	10
Upper respiratory	9
Sepsis	6
Gastrointestinal	6
Staphylococci	4
Steptococci	4
E coli	4
Other Gram negative	3
Mycoplasmas	3
CMV	3
Malaria	2
Fungal	2
Tuberculosis	2
P carinii	1
Amoebiasis	1
Other viruses	3
Other infections	6

*Note: in some patients more of one infection occurred.
CMV, cytomegalovirus; HIV, human immunodeficiency virus; HCV, hepatitis C virus; VZV, varicella-zoster virus.

DISCUSSION

aPL were originally detected in human serum by Wasserman[57] almost 100 years ago, when his complement fixation test was first used for the diagnosis of syphilis, and when the Venereal Disease Research Laboratory (VDRL) test was described.[58] A phospholipid termed cardiolipin was the major tissue extract used in this test. It was subsequently found that the VDRL was not specific for syphilis but was also positive in autoimmune diseases such as SLE. In 1983, cardiolipin was used for the first time as the antigen in a solid phase aPL specific assay by Harris *et al*,[59] and the term APS was born.[60] Syphilis was thus the first infection to be recognised as being linked to aPL. Since 1983, many other infections have been found to be associated with the presence of aPL, although a pathogenic role for these antibodies was not usually obvious except in a few isolated cases.

In 1990, it was found that the binding of the aPL to phospholipid was enhanced in autoimmune conditions by a ''cofactor'' known as β_2 glycoprotein I (β_2GPI)—a glycoprotein with anticoagulant properties—whereas the ''non''-thrombogenic aPL did not require this cofactor to enhance binding. The two types of aPL were referred to as ''autoimmune'' and ''infectious'' types.[61–64] This distinction, however, was subsequently found not to be absolute,[65–68] and it was postulated that infections may be a trigger factor for the induction of pathogenic aPL in certain predisposed individuals. In the present study, we have analysed the clinical and microbiological characteristics of 100 patients in whom pathogenic or thrombogenic aPL appeared in the course of an infectious process.

Table 4 Treatment given in 83 cases*

	n	%
Anticoagulation	61	74
Steroids	44	53
Immunoglobulins	17	20
Cyclophosphamide	10	12
Plasma exchange	10	12
Dialysis	8	10
Aspirin	6	7
Fibrinolytics	6	7
Fresh frozen plasma	5	6
Arthroplasty	3	4
Cyclosporin	2	2
Splenectomy	1	1
Other treatments	7	8

*Treatment not specified in 17 cases.

Microbial agents or viruses may induce autoimmune disease by several mechanisms. Although the specific factors resulting in the induction of aPL and the associated thrombotic events are still unknown, ''molecular mimicry'' and various infectious agents acting as superantigens have been proposed as mechanisms. Antigenic similarity between infectious agents and host tissues might result in a immune response to the shared determinant, resulting in disease. Polyclonal activation by the proteins of some infectious agents may act on particular subsets of the lymphocyte population—for example, viruses may destroy a particular T cell subset, upregulate Th1 cytokines, selectively activate other T cell subsets, and directly stimulate cytokine and chemokine release, which may influence the expression of MHC class I and class II molecules.[69–71] A hexapeptide (TLRVYK) has been identified by Blank *et al*.[72] This is specifically recognised by a pathogenic anti-β_2GPI monoclonal antibody. An evaluation of the pathogenic potential of a variety of microbial pathogens carrying sequences related to this hexapeptide in mice was carried out by the same group by infusing IgG specific to the peptide intravenously into naive mice. High titres of antipeptide anti-β_2GPI antibodies were observed in mice immunised with *H influenzae, N gonorrhoea*, and tetanus toxoid. Significant thrombocytopenia, prolonged activated partial thromboplastin times, and increased percentages of fetal loss were also observed.[72] Zhang *et al* recently identified an *S aureus* protein (Sbi) which also bound β_2GPI and could serve as a target molecule for IgG binding.[73] Gharavi *et al* showed that synthetic peptides which share both structural similarity with the putative phospholipid binding region of the β_2GPI molecule and a high homology with CMV were able to induce aPL in NIH/Swiss mice.[74 75]

Many viral infections may be accompanied by increases in aPL.[76–88] Among these, HCV[76–81] and HIV[85–88] infections have been intensively studied. In 1986, Bloom *et al* first documented lupus anticoagulant in 44% of AIDS patients and in 43% of asymptomatic HIV positive individuals (in which they may be transient).[85] The anticardiolipin antibodies described in HIV patients are of both the pathogenic (β_2GPI cofactor dependent) and the infectious type (β_2GPI independent).[86–88] As HIV infection leads to immunosuppression affecting mainly CD4+ cells and macrophages, it is possible that the pathophysiological mechanism of APS associated with HIV is different from that in other infections.

Many bacterial infections are associated with aPL. However, the increase is not usually associated with thrombotic events. Of interest, however, is the fact that—although β_2GPI dependence is usually not present in this group—in patients with leprosy (particularly in the multibacillary type of leprosy) the anticardiolipin antibodies may be β_2GPI dependent, as is found in autoimmune diseases.[89] Lucio's phenomenon is a rare manifestation of leprosy in which the histopathological findings are related to microvascular thromboses in the absence of inflammatory infiltration of the vessel walls. Levy *et al* showed that this type of leprosy was associated with β_2GPI dependency of the anticardiolipin antibodies.[90] One patient has been documented—a young adult who developed an APS in childhood following a pulmonary infection with *M pneumoniae*.[91] Streptococcal infections may also be associated with raised titres of anticardiolipin antibodies. There has been controversy over rheumatic heart disease, with some investigators reporting raised titres and others not confirming these findings.

Q fever, caused by *Coxiella burnetti*, is also associated with a high frequency of anticardiolipin antibody positivity.

Of particular interest is the unusual but potentially fatal subset of catastrophic APS.[92] Until now, more than 200 such patients have been collected in an international registry.[52 93–95] Forty patients from the present series (40%) developed catastrophic APS after infectious episodes. Several triggering factors became apparent when these cases were analysed. These included trauma, withdrawal of anticoagulation, and carcinoma, but particularly infections.[93] The latest published analysis[6] has shown that no less than 24% of catastrophic APS cases were preceded by infections. These comprised respiratory (10%), cutaneous, including infected leg ulcers (4%), urinary tract (4%), gastrointestinal (2%), general sepsis (1%), and other infections (3%). Molecular mimicry has also recently been proposed for the development of catastrophic APS following infections.[96]

Regarding treatment, in the present study we found that a wide variety of treatments had been given. Most patients received anticoagulants (74%) plus immunosuppressive or immunomodulatory treatment. Patients who received steroids had a better prognosis than those who did not. Recently, Annane *et al* showed that the use of steroids reduced the risk of death in patients with septic shock and relative adrenal insufficiency.[97] Furthermore, guidelines for the treatment of patients with catastrophic APS have recently been published[95] and include the prompt use of antibiotic cover if infection is suspected.

Conclusions

A wide variety of infections can be associated with thrombotic events in patients with APS, including the potentially lethal subset termed catastrophic APS. A disproportionately large number of patients develop catastrophic APS following infection, bearing in mind the small number of catastrophic cases documented in published reports (around 200) as opposed to the several thousand with simple/classic APS. This emphasises a major difference in the pathogenesis between the two conditions that remains to be explored in future studies, and also the need for early diagnosis and aggressive antibiotic treatment as soon as infection is suspected in a patient with APS.

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APPENDIX

CASE 1

A 42 year old white women was diagnosed with SLE 25 years ago. Over the following years she had several exacerbations of articular involvement, with progressive hand deformity (Jaccoud arthropathy) and oral ulcers that resolved with small doses of corticosteroids and non-steroidal anti-inflammatory drugs. In 1992, Libman-Sacks endocarditis and livedo reticularis were detected and laboratory tests showed the presence of lupus anticoagulant. She began treatment with acenocumarol. Six months later, she was admitted because of a urinary tract infection. Urine cultures were positive for *E coli*. She was treated with ciprofloxacin and discharged in good condition. The day after discharge, she developed epigastric pain accompanied by nausea, vomiting, diarrhoea, and fever (39℃). She had livedo reticularis and lower limb oedema and complained of upper abdominal pain (with normal peristalsis) and occasional chest discomfort. A systolic murmur was detected in the mitral valve area.

Laboratory tests revealed a marked rise in transaminases (aspartate transaminase 1313 I/U, alanine transaminase 1530 I/U), alkaline phosphatase (353 I/U), and lactic dehydrogenase (3735 I/U). The platelet count was 88×10^9/l, haemoglobin 8.8 g/l, packed cell volume 26%, white blood count (WBC) 7×10^9/l, and creatinine 1.9 mg/dl. Direct and indirect Coombs tests were positive. Peripheral blood smears showed no evidence of schistocytes. The erythrocyte sedimentation rate (ESR) was 93 mm/h, anti-ds-DNA was positive; complement levels were low (C3 = 0.117, C4<0.07, and CH50 activity = 7); 24 hour urinary protein excretion was 538 mg. IgG anticardiolipin antibodies and lupus anticoagulant were positive, with negative IgM anticardiolipin antibodies. An ECG revealed ST segment and T wave abnormalities. Echocardiography showed mitral insufficiency and a valvar vegetation. Left ventricular size and function appeared normal. There was an inferior hypokinesia. There was enzymatic evidence of a myocardial infarct (creatinine phosphokinase MB isoenzyme, 151 I/U; troponin I, 132 I/U). Coronary angiography showed 100% occlusion of the proximal right coronary artery.

A stent was inserted with good results. She started treatment with clopidogrel, aspirin, heparin, and β blockers. She was also treated with intravenous ''pulse'' methylprednisolone for the haemolytic anaemia, without improvement. Her platelet count fell to 35×10^9/l. Intravenous immunoglobulin treatment was started. Her clinical course then stabilised and a gradual improvement occurred. She was diagnosed as having catastrophic APS with renal, cardiac, and hepatic involvement associated with a urinary infection by *E Coli*.

CASE 2

The patient was a 78 year old women with an eight year history of seizures treated with oral carbamazepine. She presented with chest pain and generalised soft tissue oedema of her lower right limb. Physical examination was unremarkable except for leg pain and oedema. Laboratory investigations showed an ESR of 14 mm/h, packed cell volume 39%, haemoglobin 12.7 g/l, WBC 7480×10^9/l, platelet count 155×10^9/l, creatinine 0.8 mg/dl, anti ds-DNA negative, and antinuclear antibodies (ANA) 1/40. Urinalysis showed the presence of white cells and culture for *E coli* was positive. Ciprofloxacin treatment was given. External iliac vein and femoral thrombosis was diagnosed by the Doppler technique. Pulmonary scintigraphy showed a perfusion mismatch with a high probability of pulmonary embolism. She was diagnosed as having deep vein thromboses and pulmonary embolism. The thrombophilia tests showed positive lupus anticoagulant with negative anticardiolipin antibodies.

She began anticoagulation with heparin and acenocumarol. During the admission, she suddenly developed epileptic seizures. Computed tomography of the brain revealed lacunar infarcts. A diagnosis of primary APS associated with a urinary infection by *E coli* was made.

REFERENCES

1 **Asherson RA**. A ''primary'' antiphospholipid syndrome. *J Rheumatol* 1988;**15**:1742–4.
2 **Asherson RA**, Khamashta MA, Ordi-Ros J, *et al*. The ''primary'' antiphospholipid syndrome: major clinical and serological features. *Medicine (Baltimore)* 1989;**68**:366–76.
3 **Shoenfeld Y**, Blank M, Krause I. The relationship of antiphospholipid antibodies to infections – do they bind to infecting agents or may they even be induced by them? *Clin Exp Rheumatol* 2000;**18**:431–2.
4 **Uthman IW**, Gharavi AE. Viral infections and antiphospholipid antibodies. *Semin Arthritis Rheum* 2002;**31**:256–63.
5 **Dalekos GN**, Zachou K, Liaskos C. The antiphospholipid syndrome and infection. *Curr Rheumatol Rep* 2001;**3**:277–85.

6 **Asherson RA**, Cervera R, Piette JC, Shoenfeld Y, Espinosa G, Petri MA, *et al.* Catastrophic antiphospholipid syndrome: clues to the pathogenesis from a series of 80 patients. *Medicine (Baltimore)* 2001;**80**:355–77.
7 **Hayem G**, Kassis N, Nicaise P, Bouvet P, Andremont A, Labarre C, *et al.* Systemic lupus erythematosus associated with catastrophic antiphospholipid syndrome occurring after typhoid fever. A possible role of Salmonella lipopolysaccharide in the occurrence of diffuse vasculopathy-coagulopathy. *Arthritis Rheum* 1999;**42**:1056–61.
8 **Grinberg AR**, Heller PG, Correa G, Sarano JF, Molinas FC, Nicastro MA, *et al.* Sindrome antifosfolipido catastrófico: comunicación de dos formas de presentación. *Medicina (Buenos Aires)* 1999;**59**:743–6.
9 **Rojas-Rodríguez J**, García-Carrasco M, Ramos-Casals M, Enriquez-Coronel G, Colchero C, Cervera R, *et al.* Catastrophic antiphospholipid syndrome: clinical description and triggering factors in 8 patients. *J Rheumatol* 2000;**27**:238–40.
10 **Scully RE**, Mark EJ, McNelly W, NcNelly BU. Case records of the Massachusetts General Hospital. *N Engl J Med* 1990;**322**:754–69.
11 **Abinader A**, Hanly AJ, Lozada CJ. Catastrophic antiphospholipid syndrome associated with anti-beta-2-glycoprotein I IgA. *Rheumatology* 1999;**38**:84–5.
12 **Maddison PJ**, Thorpe C, Seale JRC, Ahmed W, Whiteley GS. Grand rounds from international lupus centres: ''catastrophic'' antiphospholipid syndrome. *Lupus* 2000;**9**:484–8.
13 **Amital H**, Levy Y, Davidson C, Lundberg I, Harju A, Kosach Y, *et al.* Catastrophic antiphospholipid syndrome: remission following leg amputation in 2 cases. *Semin Arthritis Rheum* 2001;**31**:127–32.
14 **Undas A**, Swadzba J, Undas R, Musial J. Three episodes of acute multiorgan failure in a woman with secondary antiphospholipid syndrome. *Pol Arch Med Wewn* 1998;**100**:556–60.
15 **Jou IM**, Liu MF, Chao SC. Widespread cutaneous necrosis associated with antiphospholipid syndrome. *Clin Rheumatol* 1996;**15**:394–8.
16 **Cisternas M**, Gutierrez MA, Rosenberg H, Jara A, Jacobelli S. Catastrophic antiphospholipid syndrome associated with crescentic glomerulonephritis: a clinicopathologic case. *Clin Exp Rheumatol* 2000;**18**:252–4.
17 **Scully RE**, Mark EJ, McNeely WF, Ebeling SH, Ellender SM. Case records of the Massachusetts General Hospital. *N Engl J Med* 1999;**340**:1900–8.
18 **Falcini F**, Taccetti G, Ermini M, Trapani S, Cerinic MM. Catastrophic antiphospholipid antibody syndrome in pediatric systemic lupus erythematosus. *J Rheumatol* 1997;**24**:389–92.
19 **Greisman SG**, Thayaparan RS, Godwin TA, Lockshin MD. Occlusive vasculopathy in systemic lupus erythematosus. Association with anticardiolipin antibody. *Arch Intern Med* 1991;**151**:389–92.
20 **Reitblat T**, Drogenikov T, Sigalov I, Oren S, London D. Transient anticardiolipin antibody syndrome in a patient with parvovirus B19 infection. *Am J Med* 2000;**109**:512–13.
21 **Suarez S**, Artiles J, Balda I, Melado P, Arkuch ME, Ayala A, *et al.* La tuberculosis como factor de riesgo de trombosis venosa. *An Med Inter (Madrid)* 1993;**10**:398–400.
22 **Labarca JA**, Rabaggliati RM, Radrigan FJ, Rojas PP, Perez CM, Ferres MV, *et al.* Antiphospholipid syndrome associated with cytomegalovirus infection: case report and review. *Clin Infect Dis* 1997;**24**:197–200.
23 **Cappell MS**, Simon T, Tiku M. Splenic infarction associated with anticardiolipin antibodies with acquired immunodeficiency syndrome. *Dig Dis Sci* 1993;**38**:1153–5.
24 **Manco-Johnson MJ**, Nuss R, Key N, Moertel C, Jacobson L, Meech S, *et al.* Lupus anticoagulant and protein S deficiency in children with postvaricella purpura fulminans or thrombosis. *J Pediatr* 1996;**128**:319–23.
25 **Peyton BD**, Cutler BS, Stewart FM. Spontaneous tibial artery thrombosis associated with varicella pneumonia and free protein S deficiency. *J Vasc Surg* 1998;**27**:563–7.
26 **Puri V**, Bookman A, Yeo E, Cameron R, Heathcote EJ. Antiphospholipid antibody syndrome associated with hepatitis C infection. *J Rheumatol* 1999;**26**:509–10.
27 **Uthman I**, Tabbarah Z, Gharavi AE. Hughes syndrome associated with cytomegalovirus infection. *Lupus* 1999;**8**:775–7.
28 **Viseux V**, Darnige L, Carmi E, Chaby G, Poulain JF, Cevallos R, *et al.* Pulmonary embolism and transitory anti-beta2-GPI antibodies in an adult with chicken pox. *Lupus* 2000;**9**:558–60.
29 **Leder AN**, Flansbaum B, Zandman-Goddard G, Asherson R, Shoenfeld Y. Antiphospholipid syndrome induced by HIV. *Lupus* 2001;**10**:370–4.
30 **Uthman T**, Taher A, Khalil I. Hughes syndrome associated with varicella infection. *Rheumatol Int* 2001;**20**:167–8.
31 **Creamer D**, Hunt BJ, Black MM. Widespread cutaneous necrosis occurring in association with the antiphospholipid syndrome: a report of two cases. *Br J Dermatol* 2000;**142**:1199–203.
32 **Baid S**, Pascual M, Williams WW, Tolkoff-Rubin N, Johnson SM, Collins B, *et al.* Renal thrombotic microangiopathy associated with anticardiolipin antibodies in hepatitis C-positive renal allograft recipients. *J Am Soc Nephrol* 1999;**10**:146–53.
33 **Casanova-Roman M**, Rios J, Sanchez-Porto A, Casanova-Bellido M. Deep venous thrombosis associated with pulmonary tuberculosis and transient protein S deficiency. *Scand J Infect Dis* 2002;**34**:393–4.
34 **Prieto J**, Yuste JR, Beloqui O, Civeira MP, Riezu JI, Aguirre B, *et al.* Anticardiolipin antibodies in chronic hepatitis C: implication of hepatitis C virus as the cause of the antiphospholipid syndrome. *Hepatology* 1996;**23**:199–204.
35 **D'Angelo A**, Della Valle P, Crippa L, Pattarini E, Grimaldi LM, Vigano D'Angelo S. Brief report: autoimmune protein S deficiency in a boy with severe thromboembolic disease. *N Engl J Med* 1993;**328**:1753–7.
36 **Levin M**, Eley BS, Louis J, Cohen H, Young L, Heyderman RS. Postinfectious purpura fulminans caused by an autoantibody directed against protein S. *J Pediatr* 1995;**127**:355–63.
37 **Becker DM**, Saunders TJ, Wispelway B, Schain DC. Case report: venous thromboembolism in AIDS. *Am J Med Sci* 1992;**303**:395–7.
38 **Chevalier X**, Larget-Piet B, Hernigou P, Gherardi R. Avascular necrosis of the femoral head in HIV-infected patients. *J Bone Joint Surg Br* 1993;**75B**:160.
39 **Belmonte MA**, Garcia-Portales R, Domenech I, Fernandez-Nebro A, Camps MT, De Ramon E. Avascular necrosis of bone in human immunodeficiency virus infection and antiphospholipid antibodies. *J Rheumatol* 1993;**20**:1424–8.
40 **Malnick SD**, Abend Y, Evron E, Sthoeger ZM. HCV hepatitis associated with anticardiolipin antibody and a cerebrovascular accident. Response to interferon therapy. *J Clin Gastroenterol* 1997;**24**:40–2.
41 **Gibson GE**, Gibson LE, Drage LA, Garrett CR, Gertz MA. Skin necrosis secondary to low-molecular weight heparin in a patient with antiphospholipid antibody syndrome. *J Am Acad Dermatol* 1997;**37**:855–9.
42 **Olive A**, Queralt C, Sierra G, Centelles M, Force L. Osteonecrosis and HIV infection: Osteonecrosis and HIV infection. *J Rheumatol* 1998;**25**:1243–4.
43 **Cailleux N**, Marie I, Jeanton M, Lecomte F, Levesque H, Courtois H. Are antiphospholipid antibodies pathogenic in the course of human immunodeficiency virus infection? *J Mal Vasc* 1999;**24**:53–6.
44 **Yañez A**, Cedillo L, Neyrolles O, Alonso E, Alonso E, Prevost MC, Rojas J, *et al.* Mycoplasma penetrans bacteremia and primary antiphospholipid syndrome. *Emerg Infect Dis* 1999;**5**:164–7.
45 **Padovan CS**, Pfister HW, Bense S, Fingerle V, Abele-Horn M. Detection of Mycoplasma pneumoniae DNA in cerebrospinal fluid of a patient with M. pneumoniae infection-''associated'' stroke. *Clin Infect Dis* 2001;**33**:E119–21.
46 **Korkmaz C**, Harmanci E, Metintas I, Gulbas Z. Antiphospholipid syndrome associated with intestinal amoebiasis. *Scand J Infect Dis* 2001;**33**:938–40.
47 **Nakajima T**, Kitahara H, Kono T, Ohta K, Takano T, Hasegasa R, *et al.* A surgical case of acute aortic dissection with antiphospholipid syndrome. *Jpn J Cardiovasc Surg* 2001;**30**:311–13.
48 **Turhal NS**, Peters VB, Rand JH. Antiphospholipid syndrome in HIV infection – report on four cases and review of the literature. *ACI Internat* 2001;**13**:268–71.
49 **Brown P**, Crane L. Avascular necrosis of bone in patients with human immunodeficiency virus infection: report of 6 cases and review of the literature. *Clin Infect Dis* 2001;**32**:1221–6.
50 **Ehrenfeld M**, Bar-Natan M, Sidi Y, Schwartz E. Antiphospholipid antibodies associated with severe malaria infection [abstract]. *Lupus* 2002;**11**:S611.
51 **Roldan R**, Perez-Guijo V, Anton M, Castro C, Collantes E. Two new cases of catastrophic APS in pediatric patients [abstract]. *Lupus* 2002;**11**:S618.
52 **Cervera R**, Gómez-Puerta JA, Espinosa G, Font J, De Pa Red G, Gil V, *et al.* ''CAPS Registry'': a review of 200 cases from the International Registry of patients with catastrophic antiphospholipid syndrome (CAPS) [abstract]. *Ann Rheum Dis* 2003;**62**(suppl 1):88.
53 **Olguin-Ortega L**, Jara LJ, Becerra M, Ariza R, Espinoza L, Wilson W, *et al.* Neurological involvement as a poor prognostic factor in catastrophic antiphospholipid syndrome: autopsy findings in 12 cases. *Lupus* 2003;**12**:93–8.
54 **Koschmieder S**, Miesbach W, Fauth F, Bojunga J, Scharrer I, Brodt HR. Combined plasmapheresis and immunosuppression as a rescue treatment of a patient with catastrophic antiphospholipid syndrome. *Blood Coagul Fibrinolysis* 2003;**14**:395–9.
55 **Villamil A**, Sorkin E, Basta MC, Mysler E, Macias S, Pekolj J, *et al.* Catastrophic antiphospholipid syndrome complicating orthotopic liver transplantation. *Lupus* 2003;**12**:140–3.
56 **Tattevin P**, Dupeux S, Hoff J. Leptospirosis and the antiphospholipid syndrome. *Am J Med* 2003;**114**:164.
57 **Wasserman A**. Uber Entwicklung und den Gegenwartingen Stand der Serodiagnostic Gegenuber Syphilis. *Berl Klin Wochenschr* 1907;**44**:1599–634.
58 **Michaelis L**. Precipitin reaction bei syphilis. *Berl KlinWochenschr* 1907;**44**.
59 **Harris EN**, Gharavi AE, Boey ML, Patel BM, Mackworth-Young CG, Loizou S, *et al.* Anticardiolipin antibodies: detection by radioimmunoassay and association with thrombosis in systemic lupus erythematosus. *Lancet* 1983;**ii**:1211–14.
60 **Harris EN**, Baguley E, Asherson RA, Hughes GRVH. Clinical and serological features of the ''antiphospholipid syndrome'' [abstract]. *Br J Rheumatol* 1987;**26**:19.
61 **Galli M**, Comfurius P, Maassen C, Hemker HC, de Baets MH, van Breda-Vriesman PJ, *et al.* Anticardiolipin antibodies (ACA) directed not to cardiolipin but to a plasma protein cofactor. *Lancet* 1990;**335**:1544–7.
62 **McNeil HP**, Simpson RJ, Chesterman CN, Krilis SA. Anti-phospholipid antibodies are directed against a complex antigen that includes a lipid-binding inhibitor of coagulation, β2-glycoprotein 1 (apolipoprotein H). *Proc Natl Acad Sci USA* 1990;**87**:4120–4.
63 **Matsuura E**, Igarashi Y, Fujimoto M, Ichikawa K, Koike T. Anticardiolipin cofactor(s) and differential diagnosis of autoimmune disease [letter]. *Lancet* 1990;**336**:177–8.
64 **Hunt JE**, McNeil HP, Morgan GJ, Cramer IR, Krilis SA. A phospholipid B-B2-glycoprotein I complex is an antigen for anticardiolipin antibodies occurring in autoimmune disease but not with infection. *Lupus* 1992;**1**:75–81.
65 **Elbeialy A**, Strassburger-Lorna K, Atsumi T, Bertolaccini ML, Amengual O, Hanafi M, *et al.* Antiphospholipid antibodies in leprotic patients: a correlation with disease manifestations. *Clin Exp Rheumatol* 2000;**18**:492–4.
66 **Hojnik M**, Gilburd B, Ziporen L, Blank M, Tomer Y, Scheinberg MA, *et al.* Anticardiolipin antibodies are heterogeneous in their dependency on B2-glycoporotein 1: analysis of anticardiolipin antibodies in leprosy. *Lupus* 1994;**3**:515–21.
67 **Fiallo P**, Nunzi E, Cardo PP. Beta2 glycoprotein-1-dependent anticardiolipin antibodies as risk factors for reactions in borderline leprosy patients. *Int J Lepr Other Mycobact Dis* 1998;**66**:387–8.

68 **Loizou S**, Cazabon JK, Walport MJ, Tait D, So AK. Similarities of specificity and cofactor dependence in serum antiphospholipid antibodies from patients with human parvovirus B19 infection and those with systemic lupus erythematosus. *Arthritis Rheum* 1997;**40**:103–8.
69 **Oldstone MB**. Molecular mimicry and immune-mediated diseases. *FASEB J* 1998;**80**:355–77.
70 **Karlsen AE**, Dyrberg T. Molecular mimicry between non-self, modified self and self in autoimmunity. *Semin Immunol* 1998;**10**:25–34.
71 **Albert LJ**, Inman RD. Molecular mimicry and autoimmunity. *N Engl J Med* 1999;**341**:2068–74.
72 **Blank M**, Krause I, Fridkin M, Keller N, Kopolovic J, Goldberg I, *et al*. Bacterial induction of autoantibodies to β2-glycoprotein-1 accounts for the infectious etiology of antiphospholipid syndrome. *J Clin Invest* 2002;**109**:797–804.
73 **Zhang I**, Jaconsson K, Strom K, Londberg M, Frykberg KL. Staphylococcus aureus expresses a cell surface protein that binds both IgG and B2-glycoprotein 1. *Microbiology* 1999;**145**:177–83.
74 **Gharavi EE**, Chaimovich H, Cucurull E, Celli CM, Tang H, Wilson WA, *et al*. Induction of antiphospholipid antibodies by immunization with synthetic viral and bacterial peptides. *Lupus* 1999;**8**:449–55.
75 **Gharavi AE**, Pierangeli SS, Espinola RG, Liu X, Coden-Stanfield M, Harris EN. Antiphospholipid antibodies induced in mice by immunization with a cytomegalovirus-derived peptide cause thrombosis and activation of endothelial cells in vivo. *Arthritis Rheum* 2002;**46**:545–52.
76 **Ordi-Ros J**, Villarreal J, Monegal F, Sauleda S, Estaban I, Vilardell M. Anticardiolipin antibodies in patients with chronic hepatitis C infection characterization in relation to antiphospholipid syndrome. *Clin Diagn Lab Immunol* 2000;**7**:241–4.
77 **Dalekos GN**, Kistis KG, Boumba DS, Voulgari P, Zervou EK, Drosos AA, *et al*. Increased incidence of anti-cardiolipin antibodies in patients with hepatitis C is not associated with aetiopathogenic link to antiphospholipid syndrome. *Eur J Gastroenterol Hepatol* 2000;**12**:67–74.
78 **Sthoeger ZM**, Fogel M, Smirov A, Ergas D, Lurie Y, Bass DD, *et al*. Anticardiolipin autoantibodies in serum samples and cryoglobulins of patients with chronic hepatitis C infection. *Ann Rheum Dis* 2000;**59**:483–6.
79 **Cacoub P**, Renou C, Rosenthal E, Cohen P, Loury I, Loustaud-Ratti V, *et al*. Extrahepatic manifestations associated with hepatitis C infection. A prospective multicentre study of 321 patients. *Medicine (Baltimore)* 2000;**79**:45–56.
80 **Muñoz-Rodríguez FJ**, Tàssies D, Font J, Reverter JC, Cervera R, Sánchez-Tapias JM, *et al*. Prevalence of hepatitis C virus infection in patients with antiphospholipid syndrome. *J Hepatol* 1999;**30**:770–3.
81 **Giordano P**, Galli M, Del Vecchio GC, Altomare M, Norbis F, Ruggeri L, *et al*. Lupus anticoagulant anticardiolipin antibodies and hepatitis C infection in thalassaemia. *Br J Haematol* 1998;**102**:903–6.
82 **Yamazaki M**, Asakura H, Kawamura Y, Ohka T, Endo M, Matsuda T. Transient lupus anticoagulant induced by Epstein-Barr virus infection. *Blood Coagul Fibrinolysis* 1991;**2**:771–4.
83 **Barcat D**, Constans J, Seigneur M, Guerin V, Conn C. Thrombose veineuse profonde contemporaine d'une varicelle de l'adulte. *Rev Med Interne* 1998;**27**:563–7.
84 **Faghiri Z**, Wilson WA, Taheri P, Barton EN, Morgan OS, Gharavi AE. Antibodies to cardiolipin and beta-2 glycoprotein 1 in HTLV-1-associated myelopathy/tropical spastic paraparesis. *Lupus* 1999;**8**:210–14.
85 **Bloom EJ**, Abrams DI, Rodgers G. Lupus anticoagulant in the acquired immunodeficiency syndrome. *JAMA* 1986;**258**:491–3.
86 **Asherson RA**, Shoenfeld Y. Human immunodeficiency virus infection, antiphospholipid antibodies, and the antiphospholipid syndrome. *J Rheumatol* 2003;**30**:214–19.
87 **Argov S**, Shattner Y, Burstein R, Handzel ZT, Shoenfeld Y. Autoantibodies in male homosexuals and HIV infection. *Immunol Lett* 1991;**30**:31–6.
88 **Coll J**, Gutierrez-Cebollada J, Yazbeck H, Berges A, Rubies-Prat J. Anticardiolipin antibodies and acquired immunodeficiency syndrome: prognostic marker or association with HIV infection? *Infection* 1992;**20**:140–2.
89 **Fiallo P**, Travaglino C, Nunzi E, Cardo PP. Beta-2 glycoprotein dependence of anticardiolipin antibodies in multibacillary leprosy patients. *Lepr Rev* 1998;**69**:376–81.
90 **Levy RA**, Pierangeli SA, Espinola RG. Antiphospholipid beta-2 glycoprotein 1 dependency assay to determine antibody pathogenicity [abstract]. *Arthritis Rheum* 2000;**43s**:1476.
91 **Espinosa G**, Santos E, Cervera R, Piette JC, de la Red G, Gil V, *et al*. Adrenal involvement in the antiphospholipid syndrome: clinical and immunologic characteristics of 86 patients. *Medicine (Baltimore)* 2003;**82**:106–18.
92 **Asherson RA**. The catastrophic antiphospholipid syndrome. *J Rheumatol* 1992;**19**:508–12.
93 **Asherson RA**. The pathogenesis of the catastrophic antiphospholipid syndrome. *J Clin Rheumatol* 1999;**4**:249–52.
94 **Uhtman I**, Taher A, Khalil I, Bizriu AR, Gharavi AE. Catastrophic antiphospholipid syndrome associated with typhoid fever. Comment on the article by Hayem *et al*. *Arthritis Rheum* 2002;**46**:850.
95 **Asherson RA**, Cervera R, de Groot PG, Erkan D, Boffa MC, Piette JC, *et al*. Catastrophic antiphosphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines. *Lupus* 2003;**12**:530–4.
96 **Asherson RA**, Shoenfeld Y. The role of infection in the pathogenesis of catastrophic antiphospholipid syndrome – molecular mimicry? *J Rheumatol* 2000;**27**:12–14.
97 **Annane D**, Sébille V, Charpentier C, Bollaert PE, Francois B, Korach JM, *et al*. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002;**288**:862–71.

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Concise Report

Dementia associated with the antiphospholipid syndrome: clinical and radiological characteristics of 30 patients

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***Objective*. To analyse the clinical and radiological characteristics of patients with dementia associated with the antiphospholipid syndrome (APS).**

***Methods*. Twenty-five patients were identified by a computer-assisted (MEDLINE, National Library of Medicine, Bethesda, MD) search of the literature to locate all cases of dementia associated with APS published in English, Spanish and French from 1983 to 2003. Additionally, we included five patients from our clinics.**

***Results*. There were 21 (70%) females and 9 (30%) males. The mean age of patients was 49±15 yr (range 16–79 yr). Fourteen (47%) of the patients suffered from primary APS, 9 (30%) had systemic lupus erythematosus and 7 (23%) had 'lupus-like' syndrome. Ten (33%) patients had Sneddon's syndrome and 2 (7%) had cerebral lesions described as Binswanger's disease. Other APS-related manifestations included thrombocytopenia in 12 (40%) patients, cerebrovascular accidents in 11 (37%), heart valve lesions in 8 (27%), deep vein thrombosis in 7 (28%), migraine in 7 (23%), seizures in 4 (13%); five of the 21 (24%) female patients had nine spontaneous abortions. Lupus anticoagulant was present in 21/29 (72%) patients and anticardiolipin antibodies were present in 24/29 (83%) patients. Cortical infarcts were found in 19 (63%) patients, subcortical infarcts in 9 (30%), basal ganglia infarcts in 7 (23%) and signs of cerebral atrophy in 11 (37%). Anticoagulation was used in 14/25 (56%) patients, steroids in 12/25 (48%), aspirin in 6/25 (24%) and dypiridamole in 5/25 (20%).**

***Conclusions*. Dementia is an unusual manifestation of APS but one which has a high disability impact in a patient's daily life. In order to prevent these consequences, an echocardiographic and cerebral CT or MRI evaluation are recommended in all patients with APS. Furthermore, ruling out APS should be recommended in the clinical approach to dementia, especially in young patients.**

KEY WORDS: Antiphospholipid syndrome, Dementia, Vascular dementia, Multi-infarct dementia, Sneddon's syndrome, Binswanger's disease.

Dementia is being increasingly diagnosed in clinical practice and has a high disability impact in a patient's daily life. Alzheimer's disease is the main cause of dementia, followed by vascular multi-infarct dementia, Parkinson's disease, frontal lobe dementia and, less commonly, other metabolic and reversible causes of dementia [1].

The antiphospholipid syndrome (APS) is an autoimmune prothrombotic condition characterized by venous and/or arterial thrombosis and pregnancy morbidity in the presence of antiphospholipid antibodies (aPL), i.e. lupus anticoagulant (LA) and anticardiolipin antibodies (aCL) [2]. Involvement of cerebral large vessels is frequent in APS and patients usually present clinically with transient ischaemic attacks (TIA) and strokes. However, a wide spectrum of other neurological features has been described, including chorea, epilepsy, multiple sclerosis-like lesions, psychiatric features, migraine and also dementia, among others [2, 3].

A relationship between dementia and APS has been proposed by several authors [2–7]. Although most studies have focused on patients with dementia and cerebral vascular lesions, less severe cognitive impairment has also been associated with the presence of aPL in the absence of imaging lesions in the brain [7]. Furthermore, the ischaemic stroke in Sneddon's syndrome may overlap with APS and some of these patients suffer from severe vascular dementia. The objective of this study was to analyse the clinical and radiological features of patients with dementia associated with APS, highlighting the importance of early diagnosis of this condition.

Patients and methods

Patients were identified by a computer-assisted (MEDLINE, National Library of Medicine, Bethesda, MD) search of the lit-

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TABLE 1. General characteristics of 30 patients with dementia and APS

Author	Gender/ age	Diagnosis	Associated Sneddon[a]	Other manifestation	Dementia diagnosis	aPL	CNS imaging	Treatment
1. Asherson *et al.* [12]	F/52	Lupus-like	–	LR, migraine, DVT	Simultaneously	LA, aCL+	CT: multiple hemispheric cortical infarcts	AC, S, D
2. Asherson *et al.* [12]	F/33	SLE	+	LR, migraine, DVT, AHA, TIA, chorea, VL	7 yr later	LA, aCL+	CT: multiple cortical infarcts and thalamic lacunar infarct	AC, S, D
3. Asherson *et al.* [12]	F/32	SLE	+	Migraine, LR, CVA DVT, thrombocytopenia	7 yr later	LA, aCL+	CT: multiple cortical infarcts	AC, D, ASA
4. Asherson *et al.* [12]	F/43	SLE	–	Migraine, SA (2), sup. thrombophlebitis	1.5 yr later	aCL IgG	CT: multiple bilateral small lacunar and subcortical infarcts in the frontal cand occipitalwhite matter	AC
5. Coull *et al.* [13][b]	M/59	PAPS	–	CVA, AHA, MI	Simultaneously	aCL+	CT: bilateral cortical cerebral infarcts	S
6. Coull *et al.* [13]	M/43	PAPS	–	CVA, thrombocytopenia	Simultaneously	aCL+	CT: multiple cortical and subcortical infarctions and atrophy	NR
7. Coull *et al.* [13]	M/69	PAPS	–	CVA	6 yr later	aCL+	CT: multiple small cortical infarctions and atrophy	ASA, D
8. Coull *et al.* [13]	F/28	PAPS	–	CVA	2.5 yr later	aCL+	CT: multiple cortical and subcortical infarctions	ASA, D
9. Montalbán *et al.* [14]	M/47	Lupus-like	–	Migraine, thrombocytopenia retinal vein occlusion, VL	10 yr later	LA aCL	CT: multiple cortical infarcts	AC
10. Montalbán *et al.* [14]	F/37	SLE-like	–	SA, seizure, CVA	5 yr later	LA aCL	CT: one cerebral cortical infarction	ASA
11. Asherson *et al.* [15]	M/42	Lupus-like	+	LR, MI, skin ulcers, thrombocytopenia, VL, thrombotic glaucoma	3 yr later	LA, aCL+	CT: multiple bilateral occipital and parietotemporal infarcts	S
12. Asherson *et al.* [15]	F/45	PAPS	–	Migraine	5 yr later	aCL+	CT: multiple cortical and small subcortical infarcts	AC
13. Asherson *et al.* [15]	F/42	Lupus-like	+	PE (2), LR, CVA, SA (3), VL	Simultaneously	LA, aCL	CT: multiple small cortical infarcts	AC, S
14. Westerman *et al.* [16][b]	M/54	Lupus-like	–	Thrombocytopenia	Simultaneously	aCL IgG	MRI: multiple cortical and subcortical hyperintense areas	NR
15. Charles *et al.* [17]	F/16	PAPS	+	Thrombocytopenia, LR ,VL	Simultaneously	aCL+	MRI: bilateral thalamic lesions of high signal intensity (infarctions)	NR
16. Kurita *et al.* [18]	M/39	PAPS	–	CVA	Simultaneuosly	LA+	CT: multiple brain infarcts	NR
17. Robin *et al.* [19]	F/62	SLE	–	Optic neuritis	2 yr later	LA, aCL+	CT: atrophy and subcortical low-attenuation areas MRI: hyperintensities in periventricular white matter and atrophy	S
18. Robin *et al.* [19]	F/63	SLE	–	Skin ulcers	2 yr later	LA+	CT: atrophy and subcortical low-attenuation areas. MRI: hyperintensities in periventricular white matter	S
19. Serra-Mestres [20]	M/68	PAPS	+	LR	5 yr later	aCL+	MRI: diffuse white matter hyperintensitities	NR
20. van-Horn *et al.* [21]	F/22	Lupus-like	–	Sup. thrombophlebitis, chorea	1 yr later	LA	MRI: caudate and white matter hyperintensities. SPECT: bilaterally decreased perfusion	S, ASA
21. Tomimoto *et al.* (22)	F/60	PAPS	–		Simultaneously	LA+	MRI: diffuse patchy hyperintensities in basal ganglia and cerebral white matter	
22. Rich *et al.* [23]	F/34	PAPS	+	LR, thrombocytopenia, SA, VL	Simultaneously	LA, aCL+	CT: atrophy. MRI: lacunar hyperintensities consistent with infarcts	AC
23. Fukui *et al.* [24]	F/50	SLE	–	Thrombocytopenia, retinal vein thrombosis, seizures	3 yr later	LA, aCL+	MRI: generalized and progressive, multiple hyperintensities and atrophy. SPECT: defects in bilateral temporoparietal regions	S, AC
24. Hilker *et al.* [25]	M/55	PAPS	–	DVT, thrombocytopenia	5 yr later	LA, aCL+	MRI: non-specific lacunar lesions in basal ganglia and hyperintensities in periventricular white matter, atrophy	AC, S
25. Rodríguez Campello *et al.* [26]	F/50	PAPS	+	Thrombocytopenia, LR	Simultaneously	LA, aCL+	CT: cortical and subcortical infarcts and atrophy. MRI: cortical infarcts and white matter hyperintensities	ASA
26. PC 1	F/79	PAPS	–	Thrombocytopenia, CVA DVT, PE, SA (2), migraine, seizures	1 yr later	LA	MRI: cortical, subcortical and basal ganglia infarcts, atrophy	AC
27. PC 2	F/49	Lupus-like	–	Thrombocytopenia, VL, seizures	Simultaneously	LA, aCL+	MRI: cortical and subcortical infarcts and periventricular white matter hyperintensities	S, AC
28. PC 3	F/69	SLE	–	MI, DVT, CVA	2 yr later	LA	MRI: cortical infarct in right parietal lobe	AC
29. PC 4	F/72	SLE	+	LR, thrombocytopenia, CVA, DVT, TIA	4 yr later	LA, aCL	MRI: cortical infarct in occipital lobe and atrophy	AC
30. PC 5	F/52	PAPS	–	Thrombocytopenia, VL	4 yr later	LA, aCL+	CT: cortical infarcts	S

[a]Associated Sneddon's syndrome (the co-existence of hypertension, livedo reticularis and stroke).
[b]Microthrombosis in cerebral biopsy.
Abbreviations: AC, anticoagulation; AHA, autoimmune haemolytic anaemia; ASA, aspirin; aCL, anticardiolipin antibodies; aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; CNS, central nervous system; CT, computed tomography; CVA, cerebrovascular accident; D, dypiridamole; F, female; LA, lupus anticoagulant; LR, livedo reticularis; M, male; MI, myocardial infarction; MRI, magnetic resonance imaging; NR, none reported; PAPS, primary antiphospholipid syndrome; PC, present case; PE, pulmonary embolism; S, steroids; SA, spontaneous abortions; SLE, systemic lupus erythematosus; SPECT, single-photon emission computed tomography; TIA, transient ischaemic attack; VL, valve lesions.

erature to locate all cases of APS published in English, Spanish and French from 1983 (when APS was first defined) to December 2003 (keywords used were: anticardiolipin antibodies, lupus inhibitor, cardiolipin, coagulation inhibitor, lupus anticoagulant, antiphospholipid syndrome, antiphospholipid antibodies, multi-infarct dementia, vascular dementia, Sneddon's syndrome, Alzheimer's disease and Binswanger's disease).

Cases having Sneddon's syndrome with dementia but without aPL were not included. Only cases with well-documented clinical summaries and relevant information were included in this review. Data from these cases were summarized using a standardized data form, including gender, age, diagnosis of the underlying condition, the major thrombotic clinical manifestations, immunological features, time of the evolution since the diagnosis of APS until the development of dementia, imaging features and treatment. Five new cases with dementia and APS from our clinics were added to the review. Those patients diagnosed as having dementia who were included in large APS series, but in whom no well-documented clinical data were recorded, were not considered for analysis in the present study.

Patients were defined as having dementia according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [8]. They were classified as having systemic lupus erythematosus (SLE) if they met four or more criteria of the American College of Rheumatology [9, 10], as 'lupus-like' syndrome if they met only two or three criteria and as primary APS if they met criteria of the International Consensus Statement on Preliminary Classification Criteria for definite APS, and did not meet any of the above described criteria for SLE or 'lupus-like' syndrome [11].

Ethical approval and informed patient consent were not required because the study was an analysis of patients that were located by means of a computer-assisted (MEDLINE, National Library of Medicine, Bethesda, MD) search of the literature.

Results

A total of 25 patients with dementia associated with APS were found in the literature search [12–26]. We did not include those cases where clinical, immunological and imaging characteristics were not described in detail. Five additional patients from our clinics were also reviewed.

General characteristics

General clinical features of these 30 patients are shown in Table 1. There were 21 (70%) females and 9 (30%) males. The mean age of patients was 49 ± 15 yr (range 16–79 yr). Fourteen (47%) of the patients suffered from primary APS, 9 (30%) had SLE and 7 (23%) patients had 'lupus-like' syndrome. Ten (33%) patients had Sneddon's syndrome and 2 (7%) had cerebral lesions described as Binswanger's disease.

Clinical presentation

Dementia was the presenting manifestation of the APS in 11 (37%) patients. A clinically evident past history of CVA was detected in 11 (37%) patients. Other neurological features included migraine in 7 (23%) patients, seizures in 4 (13%), TIA in 2 (7%), chorea in 2 (7%), and retinal thrombosis in 2 (7%) patients. Thrombotic glaucoma and optic neuritis were present in 1 (3%) case each. Skin involvement in the form of livedo reticularis (as a manifestation of Sneddon's syndrome) was reported in 10 (33%) patients, and skin ulcers in 3 (10%). Other APS-related manifestations were as follows: 8 (27%) patients had heart valve lesions, 7 (23%) deep-vein thrombosis (DVT), 2 (7%) pulmonary embolism, 3 (10%) myocardial infarction and 2 (7%) superficial thrombophlebitis. Previous spontaneous abortions ($n = 9$) were reported in 5 of the 21 (24%) female patients.

Laboratory profile

Twelve (40%) patients had thrombocytopenia and 2 (7%) had autoimmune haemolytic anaemia. LA was present in 21/29 (72%) patients, whilst aCL was present in 24/29 (83%) patients.

Neuroimaging features

Most patients exhibited several types of lesions on cerebral computed tomography (CT) scan or magnetic resonance imaging (MRI). Cortical infarcts were detected in 19 (63%) patients, subcortical infarcts in 9 (30%), basal ganglia infarcts in 7 (23%) and cerebral atrophy in 11 (37%). Silent brain infarcts (cerebral ischaemic lesions without any focal neurological features) were found in 14 (47%) patients.

Treatment and evolution towards dementia

Anticoagulation was used in 14/25 (56%) patients, steroids in 12/25 (48%), aspirin in 6/25 (24%) and dypiridamole in 5/25 (20%). Treatment was not reported for five cases.

In the 19 (63%) patients who presented APS manifestations previous to the diagnosis of dementia, anticoagulation had been used in 7 (37%) patients, steroids in 6 (32%), aspirin in 5 (26%) and dypiridamole in 4 (21%). The mean time of evolution from the initial APS manifestations to the diagnosis of dementia in these 19 patients was 3.5 yr (range, 1–10 yr).

Discussion

The relationship between dementia and APS has been proposed in several studies. Mosek *et al*. [6] studied 87 patients diagnosed as having dementia and compared them with 69 elderly healthy controls. They found higher levels of aPL in patients with dementia than in controls. Juby *et al*. [27] analysed the prevalence of aCL in 218 elderly patients. They disclosed that 34 patients suffered from dementia and a significant association between aCL and both vascular dementia and Alzheimer's disease was noted. Recently, Chapman *et al*. [4] studied 23 patients with primary APS and found that 13 (56%) fulfilled criteria for dementia using the Hachinski Ischemia Score (HIS). Patients with dementia were older, had more CT scan abnormalities and more electroencephalography changes than those without dementia. However, the 'Euro-Phospholipid' consortium, in their cohort of 1000 APS patients, described the presence of vascular dementia in only 25 (2.5%) cases [2]. It is possible that the higher prevalence of dementia in the Chapman *et al*. series [4] could be merely due to the small and probably highly selected group of patients studied, but it could also be due to the exclusion of SLE patients as it is know that in APS associated with SLE the incidence of neurological manifestations is higher than in primary APS [28].

The presence of aPL in patients with cognitive problems seems to be more than an epiphenomenon, as it has been demonstrated in experimental studies. Shrot *et al*. [29] performed an elegant study with BALB/c mice using a staircase test and a T maze alternation test as cognitive assessment tools. Mice immunized with anti-β2-glycoprotein I antibodies developed a higher degree of behavioural and cognitive abnormalities than those that had not been immunized.

One-third of the patients from our series had Sneddon's syndrome. Francès *et al*. [30] described a specific subset of patients with this syndrome having aPL who presented more thrombocytopenia, mitral regurgitation and irregular livedo reticularis than

patients without aPL. There is controversy concerning whether patients with Sneddon's syndrome without aPL could be a special group of transient 'seronegative' APS patients.

In the present study, almost one-third of patients had valve disease. It is well known that a high proportion of cerebral infarcts have a cardiac embolic origin and that patients with aPL have higher prevalence of valvular abnormalities [31]. Thickening of the valve leaflets is the most common lesion detected by echocardiography in both SLE and primary APS patients. The mitral valve is involved most commonly, followed by the aortic valve [32].

Epilepsy is a common neurological manifestation in APS [2]. Recent studies by Shoenfeld *et al.* [33] have confirmed a link between this manifestation and cerebrovascular involvement, heart valve lesions and livedo reticularis. In the present series, 13% of the patients with dementia presented seizures, thus reinforcing the role of focal brain ischaemic lesions in the pathogenesis of APS-related epilepsy.

Patients with dementia exhibit a wide variety of cerebral lesions on CT or MRI studies. Cortical and subcortical infarcts are the more frequent findings. Other ischaemic lesions such as lacunar and periventricular infarcts are not uncommon. Cerebral atrophy and white matter lesions (leukoaraiosis), similar to the lesions found in Binswanger's disease, are often seen, specially in elderly APS patients [15]. In SLE, these findings have been shown to be in close association with the presence of APS, but other factors, e.g. hypertension, could also contribute to their presence [34]. The continuous improvement and development of new CNS imaging techniques [i.e. positron emission tomography (PET) or single-photon emission computed tomography (SPECT)] will allow to us differentiate the distinct perfusion patterns on these cerebral disorders. Kao *et al.* [35] studied 22 patients with primary APS with only mild neuropsychiatric manifestations (headache, depression, personality disorders, memory loss and cognitive function deficits) and normal brain MRI. They found that 16 (73%) of the patients had abnormal SPECT findings, mainly diffuse hypoperfusion lesions in cerebral cortex.

It is not only those patients with evident cerebral lesions and cognitive impairment who deserve special attention, but also those patients with an asymptomatic course or subtle decline in cerebral functions having cerebral ischaemic lesions on MRI (silent brain infarcts). Vermeer *et al.* [36] followed 1077 elderly patients without dementia over 5 yr, with periodical MRI evaluation. Two hundred and seventeen (21%) patients had silent brain infarcts at baseline, with a global cognitive function significantly worse than in those patients without brain infarcts. During the follow-up, 30 (3%) of these patients developed dementia. Erkan *et al.* [5], in a 10-yr follow-up study of 66 patients with primary APS, found that 3 patients (<30 yr old) developed dementia, independently of the presence of CVA. In the present series, previous history of CVA and/or TIA was present in only 11 and 2 patients, respectively; however, silent brain infarcts were present in 14 (47%) patients.

Several strategies have been suggested for the treatment of dementia. The management of atherogenic risk factors (i.e. diabetes, hypertension, hyperlipidaemia) is crucial. However, there is still no evidence that aspirin alone is effective in treating patients with a diagnosis of dementia. In dementia associated with APS, anticoagulant treatment is required, with special care in possible everyday situations with the risk of bleeding. Furthermore, the compliance of demented patients is usually poor, which requires special thought and attention. On the other hand, prevention of dementia should be of paramount importance in those patients with a diagnosis of APS. Unfortunately, it is difficult from the present study to recommend any therapeutic strategy because patients were previously treated with a variety of medications. However, it is worth noting that the majority of patients were not on anticoagulants when the first manifestations of dementia appeared. Therefore, this reinforces the need for active antithrombotic prophylaxis once the diagnosis of APS is made.

In conclusion, dementia can be present in patients with APS in multiple scenarios, such as primary APS, Sneddon's syndrome or with white matter lesions similar to Binswanger's disease. Due to the high disability impact and prognostic consequences, we consider that an echocardiographic and cerebral CT or MRI evaluation should be recommended in all patients with APS. Also, it is important to rule out an APS in young subjects with no explicable cause of dementia, and therefore aPL should be tested in these patients in order to prevent disease progression and enable adequate treatment to begin.

Rheumatology	Key messages
	• An echocardiographic and cerebral CT or MRI evaluation are recommended in all patients with APS. • Ruling out APS should be recommended in the clinical approach to dementia.

The authors have declared no conflicts of interest.

References

1. Roman GC. Vascular dementia: distinguishing characteristics, treatment, and prevention. J Am Geriatr Soc 2003;51:S296–S304.
2. Cervera R, Piette JC, Font J *et al.* Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthritis Rheum 2002;46: 1019–27.
3. Chapman J, Rand JH, Brey RL *et al.* Non-stroke neurological syndromes associated with antiphospholipid antibodies: evaluation of clinical and experimental studies. Lupus 2003;12:514–17.
4. Chapman J, Abu-Katash M, Inzelberg R *et al.* Prevalence and clinical features of dementia associated with the antiphospholipid syndrome and circulating anticoagulants. J Neurol Sci 2002;203–204:81–4.
5. Erkan D, Yazici Y, Sobel R, Lockshin MD. Primary antiphospholipid syndrome: functional outcome after 10 years. J Rheumatol 2000;27: 2817–21.
6. Mosek A, Yust I, Treves TA, Vardinon N, Korczyn AD, Chapman J. Dementia and antiphospholipid antibodies. Dement Geriatr Cogn Disord 2000;11:33–8.
7. Sastre-Garriga J, Montalban X. APS and the brain. Lupus 2003; 12:877–82.
8. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), Washington, 1994.
9. Tan EM, Cohen AS, Fries JF *et al.* The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271–7.
10. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40:1725.
11. Wilson WA, Gharavi AE, Koike T *et al.* International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. Arthritis Rheum 1999;42:1309–11.
12. Asherson RA, Mercey D, Philips G *et al.* Recurrent stroke and multi-infarct dementia in systemic lupus erythematosus: association with antiphospholipid antibodies. Ann Rheum Dis 1987;46:605–11.
13. Coull B, Bourdette DN, Goodnight SH Jr, Briley DP, Hart R. Multiple cerebral infarctions and dementia associated with anticardiolipin antibodies. Stroke 1987;18:1107–12.
14. Montalbán J, Fernández J, Arderiu A *et al.* Demencia multiinfártica asociada a anticuerpos antifosfolípido. Presentación de dos casos. Med Clin (Barc) 1989;93:424–6.

15. Asherson RA, Khamashta MA, Gil A *et al*. Cerebrovascular disease and antiphospholipid antibodies in systemic lupus erythematosus, lupus-like disease, and the primary antiphospholipid syndrome. Am J Med 1989;86:391–9.
16. Westerman EM, Miles JM, Backnova M, Sundst W. Neuropathologic findings in multi-infarct dementia associated with anticardiolipin antibody. Arthritis Rheum 1992;35:1038–41.
17. Charles PD, Fenichel GM. Sneddon and antiphospholipid antibody syndromes causing bilateral thalamic infarction. Pediatr Neurol 1994;10:262–3.
18. Kurita A, Hasunuma T, Mochio S, Shimada T, Isogai Y, Kurahashi T. A young case with multi-infarct dementia associated with lupus anticoagulant. Intern Med 1994;33:373–5.
19. Robin C, Gonnaud PM, Durieu I *et al*. Progressive lupus dementia. 2 cases with or without antiphospholipid antibodies. Rev Neurol (Paris) 1995;151:699–707.
20. Serra-Mestres J. Antiphospholipid antibodies and Binswanger's disease. Neurology 1996;46:291–2.
21. van Horn G, Arnett FC, Dimachkie MM. Reversible dementia and chorea in a young woman with the lupus anticoagulant. Neurology 1996;46:1599–603.
22. Tomimoto H, Akiguchi I, Ohtani R, Yagi H, Ogura S, Wakita H. Effects of an antithrombin drug in patients with subacute exacerbations of Binswanger disease. Intern Med 2000;39:966–9.
23. Rich MW. Sneddon syndrome and dementia. Mayo Clin Proc 1999;74:1306.
24. Fukui T, Kawamura M, Hasegawa Y, Kato T, Kaga E. Multiple cognitive impairments associated with systemic lupus erythematosus and antiphospholipid antibody syndrome: a form of progressive vascular dementia? Eur Neurol 2000;43:115–16.
25. Hilker R, Thiel A, Geisen C, Rudolf J. Cerebral blood flow and glucose metabolism in multi-infarct-dementia related to primary antiphospholipid antibody syndrome. Lupus 2000;9:311–16.
26. Rodríguez Campello A, Roquer J, Munteis E, Gomis M, Pou A. Sneddon syndrome presenting with dementia. Neurología 2002;17: 394–5.
27. Juby A, David JA, Genge T, McElhaney J. Anticardiolipin antibodies in two elderly subpopulations. Lupus 1995;4:482–5.
28. Soltész P, Veres K, Lakos G, Kiss E, Muszbek L, Szegedi G. Evaluation of clinical and laboratory features of antiphospholipid syndrome: a retrospective study of 637 patients. Lupus 2003;12: 302–7.
29. Shrot S, Katzav A, Korczyn AD *et al*. Behavioral and cognitive deficits occur only after prolonged exposure of mice to antiphospholipid antibodies. Lupus 2002;11:736–43.
30. Francès C, Papo T, Wechsler B, Laporte JL, Biousse V, Piette JC. Sneddon syndrome with or without antiphospholipid antibodies. A comparative study in 46 patients. Medicine 1999;78:209–19.
31. Khamashta MA, Cervera R, Asherson RA *et al*. Association of antibodies against phospholipids with heart valve disease in systemic lupus erythematosus. Lancet 1990;335:1541–4.
32. Cervera R. Recent advances in antiphospholipid antibody-related valvulopathies. J Autoimmun 2000;15:123–5.
33. Shoenfeld Y, Lev S, Blatt I *et al*. Features associated with epilepsy in the antiphospholipid syndrome. J Rheumatol 2004;31:1344–8.
34. Csépány T, Bereczki D, Kollar J, Sikula J, Kiss E, Csiba L. MRI findings in central nervous system systemic lupus erythematosus are associated with immunoserological parameters and hypertension. J Neurol 2003;250:1348–54.
35. Kao CH, Lan JL, Hsieh JF *et al*. Evaluation of regional cerebral blood flow with 99mTc-HMPAO in primary antiphospholipid antibody syndrome. J Nucl Med 1999;40:1446–50.
36. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med 2003;348:1215–22.

EXTENDED REPORT

Validation of the preliminary criteria for the classification of catastrophic antiphospholipid syndrome

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Objective: To describe the characteristics of patients with catastrophic antiphospholipid syndrome (APS) included in the International Registry of patients with this condition (CAPS registry) and to analyse the value of the recently proposed preliminary criteria for the classification of catastrophic APS.
Methods: A review of the first 220 patients included in the website based CAPS registry was undertaken and the preliminary criteria for their classification were tested; 175 unselected patients with systemic lupus erythematosus or APS, or both, acted as controls.
Results: The mean age of the patients was 38 (14) years (range 7 to 74), with a female preponderance (F/M, 153/67). The main clinical manifestations included renal involvement in 154 (70%), pulmonary in 146 (66%), cerebral in 133 (60%), cardiac in 115 (52%), and cutaneous in 104 (47%); 114 patients (52%) recovered after the catastrophic APS event (mortality 48%). Patients who received the combination of anticoagulation plus steroids plus plasma exchange or intravenous immunoglobulins had the best survival rate (63%, p = 0.09). Sufficient data could be analysed for application of the classification criteria in 176 patients. According to the preliminary criteria, 89 patients (51%) could be classified as having ''definite'' and 70 (40%) as having ''probable'' catastrophic APS, thus given a sensitivity of 90.3% with a specificity of 99.4%. Positive and negative predictive values were 99.4% and 91.1%, respectively.
Conclusions: The preliminary criteria for the classification of catastrophic APS and the CAPS registry are useful tools for epidemiological studies.

In 1992, the ''catastrophic'' antiphospholipid syndrome (APS) was first defined as a potential life threatening variant of the APS which is characterised by multiple small vessel thrombosis that can lead to multiorgan failure.[1] Fortunately, this is an unusual form of presentation that represents fewer than 1% of the APS cases.[2] The recurrence rate is low with a stable clinical course if these patients are treated with adequate anticoagulation.[3] Owing to the rarity of its presentation, an international registry of patients (the CAPS registry) was created in 2000 supported by the European Forum on Antiphospholipid Antibodies (aPL).

The heterogeneity of the different clinical forms of presentation led to the need to develop consensus criteria for the classification of this condition. In 2002, a precongress workshop at the Tenth International Congress on aPL held in Taormina, Italy, allowed the establishment of the preliminary criteria for the classification of catastrophic APS that were published recently.[4] The objectives of the present study were to describe the characteristics of the patients with catastrophic APS included in the CAPS registry and to analyse the value of the preliminary criteria for their classification using the data from this registry.

METHODS

We reviewed the 220 patients who were included in the website based international registry of patients with catastrophic APS (CAPS registry) at 1 October 2003, and tested the recently proposed preliminary criteria for the classification of catastrophic APS[4] in those patients whose clinical data were sufficient for application of the criteria. The CAPS registry compiles all the published reports as well as newly diagnosed cases of catastrophic APS from all over the world. The diagnoses and data have been submitted by a wide variety of interested clinicians, but efforts were made in most cases to contact these clinicians and verify the accuracy of the data sent in. The basis for submitting patient data was clinical judgement, as no classification criteria were published until 2003. The different variables of the database are detailed at http://www.med.ub.es/MIMMUN/FORUM/CAPS.HTM.

Additionally, we analysed 175 unselected patients from our clinics as controls: 100 with systemic lupus erythematosus (SLE), classified according to the American College of Rheumatology (ACR) revised criteria[5]—all with positive aPL and 65 with associated APS—and 75 with primary APS, fulfilling the preliminary criteria for the classification of definite APS.[6]

Data analysis

Conventional Fisher's exact test was used for analysing qualitative differences. When several independent variables appeared to have statistical significance in the univariate analysis, a logistic regression test was carried out for multivariate analysis in order to rule out possible confounding variables. In this case, only those variables showing statistical significance in the multivariate analysis were considered to be significant study results. The sensitivity,

Abbreviations: aCL, anticardiolipin antibodies; ACR, American College of Rheumatology; APL, antiphospholipid antibodies; APS, antiphospholipid syndrome; CAPS, catastrophic antiphospholipid syndrome; HELLP, haemolysis, elevated liver enzymes, and low platelet count syndrome; SLE, systemic lupus erythematosus

Table 1 Previous antiphospholipid syndrome manifestations of the patients from the CAPS registry

Manifestation	n (%)
Deep vein thrombosis	44 (20)
Fetal loss	31 (20)*
Thrombocytopenia	29 (13)
Cerebrovascular accident	20 (9)
Skin ulcers	19 (9)
Pulmonary embolism	18 (8)
Livedo reticularis	17 (8)
Peripheral artery thrombosis	10 (5)
Myocardial infarction	9 (4)
Haemolytic anaemia	7 (3)
Seizures	7 (3)
Digital ischaemia	7 (3)
Valve lesions	5 (2)
No previous APS manifestations	104 (47)

*Percentage relates to the female patient population.
APS, antiphospholipid syndrome.

specificity, and predictive values of the preliminary criteria for the classification of catastrophic APS were determined according to Galen and Gambino.[7]

RESULTS

General characteristics of patients with catastrophic APS

The mean (SD) age was 38 (14) years (range 7 to 74) with a female preponderance (F/M, 153/67); 106 (48%) suffered from primary APS, 88 (40%) from SLE, 11 (5%) from lupus-like syndrome, four (2%) from rheumatoid arthritis, four (2%) from systemic sclerosis, and the remaining seven (3%) from other autoimmune disorders (relapsing polychondritis, ulcerative colitis, Crohn's disease, dermatomyositis, and Behçet's disease).

Clinical presentation and precipitating factors

Fifty three per cent of the patients had previous APS manifestations (table 1). The main previous manifestations were deep vein thrombosis in 44 (20%), fetal loss (abortions or fetal deaths) in 31 female patients (20%), thrombocytopenia in 29 (13%), cerebrovascular accidents in 20 (9%), skin ulcers in 19 (9%), pulmonary embolism in 18 (8%), and livedo reticularis in 17 (8%).

In 58% of the patients, an identifiable precipitating factor was detected, including infections (20%), surgical procedures (biopsies, dental extractions, invasive procedures, transplantation) (14%), neoplasms (9%), anticoagulation withdrawal or low international normalised ratio (INR) (7%), obstetric complications (5%), lupus flares (4%), and the use of oral contraceptives (3%). Twelve patients had two identifiable precipitating factors and in one case three triggering factors were found (anticoagulant withdrawal and surgical resection for a neoplastic process).

The majority of patients presented with multiple organ involvement at the time of catastrophic APS. The combination of pulmonary, cardiac, and renal involvement was most commonly seen. Table 2 shows the thrombotic manifestations described in these patients. However, as some types of organ involvement were detected at necropsy or during surgical procedures and other types can only be scored as present if the clinician actively looks for them, the percentages given may be an underestimate.

Laboratory findings

The following antibodies were detected: IgG anticardiolipin antibodies (aCL) in 176 of 210 patients (84%) (in 68 cases in high titres, defined according to the APS classification criteria)[6]; IgM aCL in 80 of 197 (41%) (in 20 cases in high titres and in 73 cases in association with IgG aCL); lupus anticoagulant in 154 of 203 (76%); antinuclear antibodies in 113 of 183 (62%); anti-double-stranded DNA antibodies in 60 of 168 (36%); and antibodies to extractable nuclear antigens in 29 of 128 (23%). Thrombocytopenia was found in 129 of 204 patients (63%), haemolytic anaemia in 63 of 196 (32%), disseminated intravascular coagulation (DIC) in 39 of 187 (21%), and schistocytes in peripheral smear in 21 of 174 (12%).

Table 2 Clinical manifestations at the time of presentation with catastrophic antiphospholipid syndrome in patients from the CAPS registry

Feature	n (%)
Peripheral thrombosis	**74 (34)**
Deep vein thrombosis	50 (23)
Femoral artery	8 (4)
Radial artery	4 (2)
Other arteries	19 (9)
Cerebral	**133 (60)**
Infarcts	97 (44)
Encephalopathy	17 (8)
Seizures	13 (6)
Microthrombosis	10 (5)
Venous cerebral thrombosis	5 (2)
Coma	4 (2)
Transient ischaemic attack	2 (1)
Cardiac	**115 (52)**
Valve lesion	56 (26)
Myocardial infarction	50 (23)
Heart failure	22 (10)
Microthrombosis	10 (5)
Mural thrombi	9 (4)
Pulmonary	**146 (66)**
Acute RDS	74 (34)
Pulmonary embolism	54 (24)
Pulmonary haemorrhage	16 (7)
Microthrombosis	10 (5)
Pulmonary oedema	7 (3)
Infarction	6 (3)
Abdominal	**189 (86)**
Renal	154 (70)
Hepatic	62 (28)
Splenic	41 (19)
Adrenal	33 (15)
Intestinal	27 (12)
Mesenteric	23 (11)
Pancreas	21 (10)
Portal vein thrombosis	7 (3)
Inferior cava thrombosis	7 (3)
Gallbladder thrombosis	6 (3)
Skin	**104 (47)**
Livedo reticularis	62 (28)
Skin ulcers	30 (14)
Digital ischaemia	21 (10)
Purpura	12 (6)
Necrosis	7 (3)
Microthrombosis	7 (3)
Splinter haemorrhages	5 (2)
Other manifestations	**56 (25)**
Retinal artery thrombosis	11 (5)
Bone marrow necrosis	7 (3)
Uterus	7 (3)
Neuropathy	7 (3)
Testicles	4 (2)
Retinal vein thrombosis	4 (2)
Thyroid thrombosis	3 (1)
Avascular necrosis	4 (2)
Others	8 (4)

RDS, respiratory distress syndrome.

Table 3 Treatment in the patients from the CAPS registry

Treatment	n (%)
Anticoagulation	173 (79)
Steroids	158 (71)
Cyclophosphamide	66 (30)
Plasma exchange	60 (27)
IVI	42 (19)
Dialysis	30 (14)
Fibrinolysis	8 (4)
Use of defibrotide	4 (2)
Splenectomy	3 (1)
Prostacyclin	3 (1)
Leg amputation	2 (1)
Other treatments	9 (4)

IVI, intravenous immunoglobulin.

Treatment and outcome

The different treatments used in patients with catastrophic APS are summarised in table 3. One hundred and fourteen patients (52%) recovered after the catastrophic APS event, while the remaining 106 (48%) died. Some clinical manifestations were related to a worst prognosis (death), such as renal involvement ($p = 0.004$; odds ratio (OR) = 2.4 (95% confidence interval (CI), 1.21 to 4.76)), splenic involvement ($p = 0.004$; OR = 2.63 (1.2 to 5.84)), pulmonary involvement ($p = 0.006$; OR = 1.97 (1.06 to 3.69)), SLE diagnosis ($p = 0.009$; OR = 1.9 (1.01 to 3.56)), and adrenal involvement ($p = 0.05$; OR = 2.64 (1.1 to 6.44)). Those patients who received the combination of anticoagulation plus steroids plus plasma exchange or intravenous immunoglobulins had the best survival rate (63%, $p = 0.09$).

Analysis of the preliminary criteria for classification of the catastrophic APS

Preliminary criteria for the classification of catastrophic APS are shown in table 4. From the 220 patients included in the CAPS registry, we were able to analyse enough data for criteria application in 176 patients. In the remaining cases, data on the time of development of manifestations could not be obtained accurately. One hundred and seventy one patients (97%) fulfilled the first criterion, 175 (99%) the second, 133 (76%) the third, and 159 (90%) the fourth. With respect to the number of criteria fulfilled, 89 patients (51%) fulfilled all four criteria, 74 (42%) fulfilled three, 11 (6%) fulfilled two, and two (1%) fulfilled only one criterion. According to definition of the preliminary classification criteria, 89 (51%) of the previously compiled catastrophic APS patients from the CAPS registry could be classified as having ''definite'' catastrophic APS (they fulfilled all four criteria) and 70 (40%) as having ''probable'' catastrophic APS.

The characteristics of patients classified as having ''probable'' catastrophic APS were as follows: two patients (3%) fulfilled all four criteria, except that only two organs, systems, or tissues were involved; nine (13%) fulfilled all four criteria, except for the absence of laboratory confirmation with at least six weeks owing to the early death of a patient never tested for aPL before the catastrophic APS; and 59 (84%) fulfilled criteria 1, 2, and 4.

Only one patient from the control group fulfilled criteria for ''probable'' catastrophic APS. According to these findings, the sensitivity of the preliminary criteria for the classification of catastrophic APS is 90.3%, the specificity 99.4%, the positive predictive value 99.4%, and the negative predictive value 91.1%.

DISCUSSION

Over the last 10 years, various different case reports and small series have described patients with catastrophic APS. Two major paper summarised the different characteristics of a total of 130 patients and provided information on the pathogenesis, clinical features, treatment, and outcome.[8 9] The website based CAPS registry has also compiled a large amount of information but the present study indicates that additional efforts should be made in the future because the registry often receives insufficient data or information on patients who do not have ''definite'' or ''probable'' catastrophic APS from physicians all over the world.

Recognition of catastrophic APS has increased over the past years, and it is now clear that it is not only associated with SLE or primary APS, but also with other autoimmune conditions such as rheumatoid arthritis, systemic sclerosis, intestinal inflammatory diseases, and Behçet's disease, among others. Despite earlier recognition and better knowledge of the pathophysiology, the mortality rate is still unacceptably high (48%), specially in SLE patients and in patients with cardiac, pulmonary, renal, splenic, and adrenal involvement.

Table 4 Preliminary criteria for the classification of catastrophic antiphospholipid syndrome[4]

(1) Evidence of involvement of three or more organs, systems, and/or tissues*
(2) Development of manifestations simultaneously or in less than one week
(3) Confirmation by histopathology of small vessel occlusion in at least one organ or tissue†
(4) Laboratory confirmation of the presence of antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies)‡
Definite catastrophic APS: all four criteria
Probable catastrophic APS—any of the following:
(a) All four criteria, except for only two organs, systems, and/or tissues involved
(b) All four criteria, except for the absence of laboratory confirmation (within at least 6 weeks) owing to the early death of a patient never tested for aPL before the catastrophic APS
(c) Criteria (1), (2), and (4)
(d) Criteria (1), (3), and (4) and the development of a third event between one week and one month after presentation, despite anticoagulation

*Usually clinical evidence of vessel occlusions, confirmed by imaging techniques when appropriate. Renal involvement is defined by a 50% rise in serum creatinine, severe systemic hypertension (>180/100 mm Hg). and/or proteinuria (>500 mg/24 hours).
†For histopathological confirmation, significant evidence of thrombosis must be present, although vasculitis may coexist occasionally.
‡If the patient had not previously been diagnosed as having an APS, the laboratory confirmation requires that the presence of antiphospholipid antibodies must be detected on two or more occasions at least six weeks apart (not necessarily at the time of the event), according to the proposed preliminary criteria for the classification of definite APS.

Recently, Erkan *et al*[3] evaluated the clinical outcome of 58 survivors of a catastrophic APS event. Thirty eight patients (66%) did not develop further APS related events, 15 (26%) developed a new thrombotic episode (in 13 cases during anticoagulation therapy), but none of them developed further catastrophic APS episodes.

The clinical approach to the treatment of catastrophic APS will depend on the site and extension of the vascular occlusions and the degree of systemic inflammatory response. The cornerstone of the treatment includes readiness to suspect the condition and the treatment of any precipitating factor, especially adequate antibiotic therapy for related infections based on the clinical setting, appropriate anticoagulant management, and the use of immunosuppressive drugs (especially steroids), plus third line therapy (plasma exchange or intravenous immunoglubulins) for the treatment of the thrombotic and cytokine "storm".[4] Finally, a series of life support measures are needed, such as mechanical ventilation, inotropic drugs, and continuous haemodialysis.[10]

The differential diagnosis in some circumstances is very difficult, specially with other microangiopathic syndromes that are capable of producing multiorgan thrombotic events. These conditions include thrombotic thrombocytopenic purpura, haemolytic-uraemic syndrome, heparin induced thrombocytopenia, and the HELLP (haemolysis, elevated liver enzymes, and low platelet count) syndrome.[11] In these critically ill patients there is a high chance that their blood samples may show false positive results in lupus anticoagulant assays (for example, coagulation factor deficiencies or heparin use), or that treatment decisions have to be made before the results of laboratory tests are available. However, the presence of persistent positive levels of aPL in a patient with these conditions will lead to the diagnosis of concomitant catastrophic APS. In fact, several patients in the CAPS registry fulfilled criteria for thrombocytopenic purpura or HELLP as well. Thus we only analysed patients with aPL as controls—including both SLE and primary APS patients—and for this reason we did not include controls with multiorgan thrombotic events (for example, thrombotic thrombocytopenic purpura, haemolytic-uraemic syndrome, or HELLP) but without aPL.

Though microthrombosis is one of the typical markers of a catastrophic APS event, it may be difficult to confirm, and many patients could only be labelled as "probable" catastrophic APS based on large vessel multiorgan thrombotic involvement over a short period of time in the presence of aPL. Because of these difficulties in the confirmation of a definite catastrophic APS event, we included both "definite" and "probable" catastrophic APS in the evaluation of the classification criteria. According to our results, the International Consensus Statement on Preliminary Classification Criteria for the catastrophic APS is a useful tool for epidemiological studies and it is hoped that these criteria will be tested in future prospective multicentre studies, and that modifications or additions to the criteria will be made at subsequent workshops. It should be emphasised that these criteria are mostly empirical and have been accepted for classification purposes only. They are not intended to be used as strict diagnostic criteria in a given patient.

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APPENDIX

THE CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME REGISTRY PROJECT GROUP

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REFERENCES

1 **Asherson RA**. The catastrophic antiphospholipid syndrome. *J Rheumatol* 1992;**19**:508–12.
2 **Cervera R**, Piette JC, Font J, Khamashta MA, Shoenfeld Y, Camps MT, *et al*. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1000 patients. *Arthritis Rheum* 2002;**46**:1019–27.
3 **Erkan D**, Asherson RA, Espinosa G, Cervera R, Font J, Piette JC, *et al*. Long term outcome of catastrophic antiphospholipid syndrome survivors. *Ann Rheum Dis* 2003;**62**:530–3.
4 **Asherson RA**, Cervera R, de Groot PG, Erkan D, Boffa MC, Piette JC, *et al*. Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines. *Lupus* 2003;**12**:530–4.
5 **Tan EM**, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, *et al*. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;**25**:1271–7.
6 **Wilson WA**, Gharavi AE, Koike T, Lockshin MD, Branch DW, Piette JC, *et al*. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. *Arthritis Rheum* 1999;**42**:1309–11.
7 **Galen RS**, Gambino RS. *Beyond normality: the predictive value and efficiency of medical diagnoses*. New York: John Wiley, 1975.
8 **Asherson RA**, Cervera R, Piette JC, Font J, Lie JT, Burcoglu A, *et al*. Catastrophic antiphospholipid syndrome. Clinical and laboratory features of 50 patients. *Medicine (Baltimore)* 1998;**77**:195–207.
9 **Asherson RA**, Cervera R, Piette JC, Shoenfeld Y, Espinosa G, Petri MA, *et al*. Catastrophic antiphospholipid syndrome: clues to the pathogenesis from a series of 80 patients. *Medicine (Baltimore)* 2001;**80**:355–77.
10 **Westney GE**, Harris EN. Catastrophic antiphospholipid syndrome in the intensive care unit. *Crit Care Clin* 2002;**18**:805–17.
11 **Asherson RA**, Cervera R. Catastrophic antiphospholipid syndrome. *Curr Opin Hematol* 2000;**7**:325–9.

CONCISE REPORT

Disseminated intravascular coagulation in catastrophic antiphospholipid syndrome: clinical and haematological characteristics of 23 patients

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Background: Disseminated intravascular coagulation (DIC) is an acquired syndrome characterised by formation of microthombi and fibrin deposition in the microvasculature. The catastrophic antiphospholipid syndrome (APS) is characterised by multiorgan thrombosis, mainly involving small vessels. A broad spectrum of disorders may develop DIC features; however, the catastrophic APS has not previously been recognised as a cause of DIC.

Objective: To analyse the clinical and laboratory characteristics of catastrophic APS patients with DIC features.

Methods: The web site based international registry of patients with catastrophic APS (CAPS registry) (http://www.med.ub.es/MIMMUN/FORUM/CAPS.HTM) was analysed and the cases with DIC features selected.

Results: In 173 patients with catastrophic APS, 23 (13%) were found with DIC features. The clinical and immunological characteristics were similar in catastrophic APS patients with and without DIC features; a significant difference was found only in the prevalence of thrombocytopenia (100% in patients with DIC features *v* 59% in those without DIC features).

Conclusions: DIC features are not rare in catastrophic APS, supporting the need for systematic screening of antiphospholipid antibodies in all patients with DIC features without precipitating factors. The presence of DIC features in the context of an APS makes it imperative to rule out the catastrophic variant of this syndrome.

Disseminated intravascular coagulation (DIC) is an acquired syndrome characterised by the widespread activation of coagulation with occlusion of small and medium sized vessels. This condition may compromise the blood supply to organs and contribute to multiorgan failure. It is not a disease entity in itself but always occurs as a complication of an underlying disorder, the most common being infection, severe trauma, malignancy, and obstetric complications.[1–3]

The "catastrophic" variant of the antiphospholipid syndrome (APS) is an accelerated form of this syndrome resulting in multiorgan failure because of multiple small vessel occlusions.[4] As with DIC, most of the catastrophic APS episodes are preceded by a precipitating event, such as infection, surgery or trauma, obstetric complications, and malignancies.[5 6] Furthermore, laboratory features of DIC were reported in 19–28% of the largest catastrophic APS series.[7 8]

Our objective in the present study was to analyse the clinical and laboratory characteristics of catastrophic APS patients with DIC features to determine whether these patients form a special subset within the catastrophic APS population.

METHODS

We analysed the web site based international registry of patients with catastrophic APS (the CAPS registry; http://www.med.ub.es/MIMMUN/FORUM/CAPS.HTM). This registry was created in 2000 by the European Forum on Antiphospholipid Antibodies and compiles all the published reports as well as newly diagnosed cases from all over the world. Up to October 2003 it included 220 patients with this condition.[9] We selected those patients who had some of the laboratory features of DIC (raised fibrin related markers, decreased fibrinogen concentrations, or both). Isolated thrombocytopenia and prolonged prothrombin time were not considered to be selection criteria as they can be manifestations of the APS.

According to the International Scientific Subcommittee for DIC, we calculated the DIC score as follows:

- platelets: $>100\times10^9$/l = 0; $<100\times10^9$/l = 1; $<50\times10^9$/l = 2;
- raised fibrin related markers (fibrin degradation products and D-dimers): no increase = 0; moderate increase = 2; marked increase = 3;
- prolonged prothrombin time: <3′ seconds = 0, 3–6 seconds = 1; >6 seconds = 2;
- decreased fibrinogen: >1.0 g/l = 0; <1.0 g/l = 1.

Overt DIC was diagnosed when the total score was ⩾5; a score <5 was considered suggestive of DIC.[10]

Fisher's exact test (bilateral) was employed for the statistical analysis, using the SPSS 10.0 statistical program.

RESULTS

General characteristics

Of the 220 patients included in the CAPS registry, information on DIC features was not available in 34 cases and there were incomplete data for DIC scoring in 10 further patients. This left a total of 176 patients available for analysis. Of these, 23 (13%) had DIC features associated with catastrophic APS: 17 (74%) female and six (30%) male, mean (SD) age 39 (13) years (range 11 to 60). Ten (43%) suffered from primary APS, nine (39%) had systemic lupus erythematosus (SLE), three (13%) had lupus-like disease, and one (4%) had polychondritis.

Abbreviations: aCL, anticardiolipin antibodies; APS, antiphospholipid syndrome; DIC, disseminated intravascular coagulation

Table 1 Laboratory variables according the scoring system for DIC

Case	Platelets ($\times 10^9$/l)	Score	FDPs	D-dimers	Score	PT (s)	Score	Fibrinogen (g/l)	Score	Total
1	128	0	Increased	NR	3	13.6	0	4.98	0	3
2	57	1	Increased	NR	3	12.7	0	6.5	0	4
3	39	2	NR	Increased	3	NR	NA	1.27	0	5
4	21	2	Increased	Increased	2	NR	NA	Low	1	5
5	67	1	Increased	NR	2	NR	NA	0.84	1	4
6	80	1	Increased	NR	3	32	2	0.7	1	7
7	47	2	Increased	NR	2	NR	NA	4.0	0	4
8	50	2	Increased	NR	3	NR	NA	1.8	0	5
9	"Low"	NA	NR	Increased	2	NR	NA	Low	1	3
10	12	2	Increased	NR	2	19	2	6.49	0	6
11	35	2	Increased	NR	2	10.4	0	0.0024	1	5
12	57	1	Increased	NR	3	42	2	NR	NA	6
13	34	2	Increased	Increased	3	16.7	2	4.6	0	7
14	16	2	Increased	NR	2	Prolonged	1	NR	NA	5
15	16	2	Increased	Normal	2	NR	NA	NR	NA	4
16	86	1	Increased	NR	2	NR	NA	NR	NA	3
17	31	2	NR	Increased	2	Prolonged	1	4.65	0	5
18	127	0	Increased	Increased	3	NR	NA	3.12	0	3
19	77	1	Increased	NR	2	NR	NA	NR	NA	3
20	61	1	Increased	NR	3	NR	NA	NR	NA	4
21	16	2	Increased	NR	3	NR	NA	5.51	0	5
22	70	1	Increased	Increased	2	NR	NA	NR	NA	3
23	35	2	NR	Increased	2	Normal	0	NR	NA	4

Platelet count: $>100\times10^9$/l = 0; $<100\times10^9$/l = 1; $<50\times10^9$/l = 2.
Raised fibrin related markers (FDPs and D-dimers): no increase = 0; moderate increase (raised but less than twice the normal level) = 2; marked increase (more than twice the normal level) = 3.
Prothrombin time: <3 seconds = 0; 3–6 seconds = 1; >6 seconds = 2.
Fibrinogen concentration: >1.0 g/l = 0; <1.0 g/l = 1.
Total score: ⩾5, compatible with DIC; <5, suggestive of DIC.
DIC, disseminated intravascular coagulation; FDPs, fibrinogen degradation products; NA, not available; NR, not recorded; PT, prothrombin time.

Clinical presentation and precipitating factors

Intra-abdominal involvement was identified in all 23 patients, mainly consisting of renal (78%), hepatic (48%), gastrointestinal (39%), splenic (17%), pancreatic (9%), and adrenal (9%) manifestations.

Pulmonary complications were reported in 16 patients (70%), mainly acute respiratory distress syndrome (ARDS) and confirmed pulmonary embolism, but occasionally intra-alveolar haemorrhage. Eleven patients (48%) had cardiac involvement, mainly cardiac failure and confirmed myocardial infarction or valve lesions. Fifteen patients (65%) had evidence of cerebrovascular complications, mainly encephalopathy and cerebrovascular accidents, but occasionally seizures, headache, or silent brain infarcts. Deep venous thrombosis was present in two patients (9%) and peripheral arterial occlusive disease in one (4%).

Skin manifestations were also frequent (78%) and consisted of livedo reticularis, ulcers, necrotic lesions, digital gangrene, purpura, microthrombosis of small vessels, splinter haemorrhages, and multiple ecchymosis.

Other lesions occasionally encountered were bone marrow necrosis, mononeuritis multiplex, and retinal involvement.

The most common precipitating conditions were infections (seven cases) and surgical procedures (four cases). Other cases were attributed to drug use and anticoagulation withdrawal (one each).

APS related laboratory findings

Thrombocytopenia (platelet count $<150\times10^9$/l) was reported in all 23 patients and evidence of haemolytic anaemia in nine (41%), accompanied by schistocytes in five (23%). The IgG isotype of anticardiolipin antibodies (aCL) was detected in 19 patients (83%), IgM aCL in eight (38%), and lupus anticoagulant in 18 (82%).

DIC features

A platelet count of $<100\times10^9$/l was reported in 20 patients (87%) (in one additional case, the count was reported only non-specifically, as "low platelet count"). Increased fibrin degradation products were reported in all 19 patients in whom they were recorded, and positivity for D-dimers in eight of nine cases (89%). A prolonged prothrombin time was reported in six of 10 patients (60%) and decreased fibrinogen levels were present in five of 13 cases (39%) (in two cases they were reported non-specifically as "low levels"). Table 1 shows in detail each case of catastrophic APS with DIC features. Eleven patients (48%) had a DIC score of 5 or above (compatible with overt DIC). The remaining 12 patients (52%) had a DIC score of 3 or 4 (suggestive of DIC).

Treatment and outcome

Most patients received a combination of treatments. Anticoagulation were used in 20 patients (87%), steroids in 19 (83%), plasma exchange in nine (39%), cyclophosphamide in eight (35%), intravenous gamma globulin in five (22%), and splenectomy in two (9%). Other treatments used were prostacyclin and antithrombin concentrate (one case each).

Recovery occurred in 61% of catastrophic APS patients with DIC features and in 58% of those without DIC features (NS). Assessing the use of single treatments, recovery of DIC patients occurred in 58% of those treated with anticoagulants *v* 67% of those not treated with anticoagulants (NS); in 58% of those treated with steroids *v* 67% of those not (NS); in 38% of those treated with cyclophosphamide *v* 71% of those not (NS); in 50% of those treated with plasmapheresis *v* 64% of those not (NS); and in 83% of those treated with intravenous gamma globulin *v* 50% of those not (NS).

Comparison of catastrophic APS patients with and without DIC

The profiles of demographic characteristics (sex distribution and mean age), clinical features (severe organ involvement), and immunological findings (lupus anticoagulant, IgG aCL, and IgM aCL) were similar. Significant differences were found only in the prevalence of thrombocytopenia (100% in the DIC group *v* 59% in the catastrophic APS patients without

Table 2 Differential diagnosis of multiorgan thrombotic disorders

	Catastrophic APS	DIC	TMHA
Haemorrhagic manifestations	–	+	±
Anaemia	±	±	+
Schistocytes	±	±	++
Thrombocytopenia	++	++	+++
Prolonged prothrombin time	–	+	–
Prolonged activated partial thromboplastin time	±	+	–
Fibrinogen degradation products	±	+	–
Antiphospholipid antibodies	++	±	±
Plasma ADAMTS-13 activity	Normal?	Moderately reduced	Absent* or severely reduced

*In cases of familial thrombocytopenic purpura (TTP), acquired idiopathic TTP, and pregnancy related TTP.
ADAMTS-13, von Willebrand factor cleaving protease; APS, antiphospholipid syndrome; DIC, disseminated intravascular coagulation; TMHA, thrombotic microangiopathic haemolytic anaemia.

DIC, $p<0.001$). Other characteristics typically encountered in other states causing DIC—such as renal failure, skin involvement, or ARDS—were not more frequent in catastrophic APS patients with DIC features than in those without.

DISCUSSION

We observed laboratory features of DIC in at least 13% of patients diagnosed as having the catastrophic variant of APS. However, it should be borne in mind that there were incomplete data for DIC scoring in 10 reported cases. Thus, under ideal circumstances where all the data were available, the incidence might turn out to be higher.

The pathophysiology of DIC and catastrophic APS is poorly understood, but the two conditions probably share some pathogenic mechanisms and triggering factors. In DIC, enhanced fibrin formation is caused by tissue factor mediated thrombin generation and simultaneous dysfunction of inhibitory mechanisms, such as the antithrombin system and the protein C and protein S system. In addition, fibrin removal is impaired because of fibrinolytic system depression, mainly caused by high circulating levels of plasminogen activator inhibitor type 1 (PAI-1).[1–3] Conversely, catastrophic APS is associated with endothelial cell activation as a result of antigen–antibody reactions on the surface of endothelial cells or monocytes.[11] Furthermore, inhibition of both protein C activation and the function of activated protein C have been observed in association with APS.[12] Finally, increased plasma concentrations of PAI-1 characterise the hypofibrinolytic state in APS.[13]

A link between DIC and catastrophic APS can be assumed from the original description of DIC by McKay in 1965.[14] He described a 38 year old woman with SLE with some features suggestive of APS, such as chorea, mitral valve disease, and spontaneous abortion. A few days after an elective cholecystectomy she developed a sudden episode of multiorgan failure characterised by fever, severe congestive heart failure, ARDS, renal failure, and somnolence accompanied by features of DIC (low fibrinogen, thrombocytopenia, and a prolonged prothrombin time). Her clinical status deteriorated and she died three weeks after the surgical procedure. Necropsy showed microvascular thrombosis of the heart, adrenal glands, lungs, and bone marrow, in addition to a non-bacterial thrombotic endocarditis, all of these being typical features of catastrophic APS. At that time, however, APS was an unknown entity.

Infections associated with DIC were the most common precipitating factors in catastrophic APS in our series of patients. Molecular ''mimicry'' has been proposed as one of the major mechanisms responsible for the development of catastrophic APS following infections.[15] Thus an infectious aetiology for the APS, especially its catastrophic variant, should perhaps be considered more frequently and appropriate antibiotic therapy instituted.

Another aspect to bear in mind is the differential diagnosis between DIC and disorders presenting with thrombotic microangiopathic haemolytic anaemia (TMHA). The clinical picture of DIC, TMHA, and APS may overlap and, if they coexist in the same patient, the diagnosis may be difficult at the time of presentation (table 2).

In conclusion, DIC features are not rare in catastrophic APS. This would support the need for systematic screening of antiphospholipid antibodies in all patients with DIC without precipitating factors. In addition, the presence of DIC in the context of an APS makes it mandatory to rule out the catastrophic variant of this syndrome.

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APPENDIX

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REFERENCES

1 **Levi M**, de Jonge E, van der Poll T, ten Cate H. Advances in the understanding of the pathogenetic pathways of disseminated intravascular coagulation result in more insight in the clinical picture and better management strategies. *Semin Thromb Hemost* 2001;**27**:569–75.
2 **Levi M**, ten Cate H. Disseminated intravascular coagulation. *N Engl J Med* 1999;**341**:586–92.
3 **Muller-Berghaus G**, ten Cate H, Levi M. Disseminated intravascular coagulation: clinical spectrum and established as well as new diagnostic approaches. *Thromb Haemost* 1999;**82**:706–12.
4 **Asherson RA**. The catastrophic antiphospholipid syndrome. *J Rheumatol* 1992;**19**:508–12.
5 **Cervera R**, Piette J-C, Font J, Khamashta MA, Shoenfeld Y, Camps MT, *et al.* Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. *Arthritis Rheum* 2002;**46**:1019–27.
6 **Asherson RA**, Cervera R, de Groot PG, Erkan D, Boffa M-C, Piette J-C, *et al.* Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines. *Lupus* 2003;**12**:530–4.
7 **Asherson RA**, Cervera R, Piette J-C, Font J, Lie JT, Burcoglu A, *et al.* Catastrophic antiphospholipid syndrome: clinical and laboratory features of 50 patients. *Medicine (Baltimore)* 1998;**77**:195–207.
8 **Asherson RA**, Cervera R, Piette J-C, Shoenfeld Y, Espinosa G, Petri MA, *et al.* Catastrophic antiphospholipid syndrome. Clues to the pathogenesis from a series of 80 patients. *Medicine (Baltimore)* 2001;**80**:355–77.
9 **Cervera R**, Gomez-Puerta JA, Espinosa G, Cucho M, Font J. ''CAPS registry'': a review of 200 cases from the international registry of patients with catastrophic antiphospholipid syndrome (CAPS). *Ann Rheum Dis* 2003;**62**(suppl 1):88.
10 **Taylor FB**, Toh CH, Hoots WK, Wada H, Levi M. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. *Thromb Haemost* 2001;**86**:1327–30.
11 **Triplett DA**, Asherson RA. Pathophysiology of the catastrophic antiphospholipid syndrome (CAPS). *Am J Hematol* 2000;**65**:154–9.
12 **De Groot PG**, Horbach DA, Derksen RHWM. Protein C and other cofactors involved in the binding of antiphospholipid antibodies: relation to the pathogenesis of thrombosis. *Lupus* 1996;**5**:488–93.
13 **Tassies D**, Espinosa G, Munoz-Rodriguez FJ, Freire C, Cervera R, Monteagudo J, *et al.* The 4G/5G polymorphism of the type 1 plasminogen activator inhibitor gene and thrombosis in patients with antiphospholipid syndrome. *Arthritis Rheum* 2000;**43**:2349–58.
14 **McKay DG**. Diseases of hypersensitivity: disseminated intravascular coagulation. *Arch Intern Med* 1965;**116**:83–94.
15 **Asherson RA**, Shoenfeld Y. The role of infection in the pathogenesis of catastrophic antiphospholipid syndrome – molecular mimicry? *J Rheumatol* 2000;**27**:12–14.

MAJOR ARTICLE

Recurrent Pulmonary Thromboembolism in a Patient with Systemic Lupus Erythematosus and HIV-1 Infection Associated with the Presence of Antibodies to Prothrombin: A Case Report

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Background. The coexistence of human immunodeficiency virus (HIV) infection and systemic lupus erythematosus (SLE) is being increasingly reported and, because of the immunological disturbances demonstrated in HIV-infected patients, diagnostic and therapeutic difficulties may arise when the 2 conditions coexist. Antiphospholipid antibodies are demonstrable in patients with both conditions, but clinical manifestations of the antiphospholipid syndrome (APS) in HIV-infected patients, although reported, are uncommon.

Methods. We describe a patient with HIV infection and SLE who manifested 4 episodes of deep vein thrombosis (DVT) complicated by pulmonary embolism. Enzyme-linked immunosorbant assay was used to test for the presence of antiphospholipid antibodies, including anticardiolipin antibodies, anti–β2-glycoprotein 1 antibodies, and antiprothrombin antibodies (anti-PT). Additionally, we performed a computer-assisted search of the literature (via the Medline database) to identify all reported cases of HIV infection plus SLE.

Results. We document the case of 35-year-old African woman with HIV infection and SLE who developed recurrent episodes of DVT and pulmonary embolism in the presence of anti-PT and discuss in depth the pathogenic role of these antibodies and the clinical challenges posed to clinicians by the coexistence of HIV and SLE in the same patient.

Conclusions. Immunological reconstitution in HIV-infected patients contributes to the appearance of multiple autoimmune conditions, including SLE and APS. The recognition of the coexistence of these autoimmune disorders in HIV-infected patients has important implications in the treatment of and prognosis for these individuals.

Since the introduction of HAART in the late 1990s, the clinical spectrum of HIV infection has changed dramatically. During the past few years, increased recognition of a variety of autoimmune disturbances has emerged because of better control of HIV disease, which is associated with the constant antigenic viral stimulation and immune reconstitution that follows an increase in the number of circulating $CD4^+$ cells [1]. Some of these disorders, such as inflammatory myopathies, systemic vasculitis, and systemic lupus erythematosus (SLE), may coexist with and overlap with the underlying HIV infection.

Several chronic viral infections (such as those due to HIV, hepatitis C virus, and cytomegalovirus) have been shown to generate widely different types of autoantibodies, including antiphospholipid antibody, that are capable of inducing (in some circumstances) thrombosis, as has been observed in patients with antiphospholipid syndrome (APS) [2]. We describe a 35-year-old African woman with HIV infection and SLE who developed recurrent episodes of deep vein thrombosis and pulmonary embolism in the presence of antiprothrombin antibody (anti-PT), and we discuss in depth the pathogenic role of these antibodies and the clinical challenges posed to clinicians by the coexistence of HIV and SLE in the same patient.

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CASE REPORT

The patient, a 35-year-old African woman, received a diagnosis of HIV-1 infection in 1996 and was being treated with a combination of efavirenz, zidovudine, and lamivudine. There were no concomitant infections present at the time of referral. Between October and December 2002, the patient was admitted to hospital on 4 separate occasions with recurrent lower limb deep vein thromboses complicated by pulmonary emboli. It was noted during this period that she had developed symmetrical nonerosive arthritis in the hands and knees accompanied by progressive hemolytic anemia.

Serological investigations showed antinuclear antibody titers of 1:640 and detected antibodies to extractable nuclear antigens (i.e., anti-Smith antibodies, antiribonucleoprotein antibodies, and anti–Sjögren syndrome A/Ro antibodies). Additionally, the level of the C4 component of complement was reduced to <10 mg/dL (normal range, 10–34 mg/dL), results of the Coombs test were positive, and the erythrocyte sedimentation rate was elevated at 97 mm/h. The patient received a diagnosis of SLE, and high-dose oral steroids were added to her regimen once transfusion resulted in a hemoglobin level of 15 mg/dL. Steroid treatment was gradually tapered to a maintenance level of 5 mg daily, and there was no further decrease in the hemoglobin level during the subsequent 3-year period. Long-term antimalarial therapy was also added to her regimen (chloroquine, 200 mg daily).

Results of ELISA (Cheshire Diagnostics) for detection of anticardiolipin antibody (aCL) and anti–β2-glycoprotein 1 antibody (β2GP1) were negative on several occasions. Results of solid-phase ELISA (Cheshire Diagnostics) for detection of anti-PT were positive, and anti-PT levels remained elevated during each the following 2 years (means of 25.3 AEU during the first year and 30.3 AEU during the second year; normal level, <12 AEU). Despite achievement of an international normalized ratio of $\geqslant$3 during anticoagulation therapy, she nevertheless had 3 additional peripheral venous thromboses, all of which were complicated by pulmonary emboli. Each thrombosis episode was treated with unfractionated heparin and required hospital admission. The level of anti-PT diminished after receipt of appropriate therapy for HIV infection for 2 years; however, titers of β2GP1 became positive 6 months later in 2004.

At the time of writing, the patient has remained healthy while receiving the antiretroviral regimen specified above, warfarin (international normalized ratio, 2.5–3), antimalarial treatment (chloroquine phosphate, 200 mg daily), and prednisone (5 mg daily). The hemoglobin level has remained stable, with an HIV load of <50 copies/mL and a $CD4^+$ cell count of 260 cells/mm^3. She is working full-time.

DISCUSSION

Thrombosis and HIV infection. Patients with HIV infection have an increased risk of thrombosis, with an incidence as high as 8% reported in one series [3]. The causes of thrombosis in patients with HIV infection include opportunistic infection (mainly that due to cytomegalovirus), related malignancies, receipt of drugs (e.g., protease inhibitors, abacavir, and megestrol acetate), injection drug use, acquired hematological disorders (protein S and protein C deficiency, protein C resistance with factor V Leiden mutation, lupus anticoagulant positivity, and aCL), and HIV infection itself. Additionally, there is a significant correlation between thrombotic disease and a $CD4^+$ cell count of <200 cells/mm^3 [4–7].

Antiphospholipid and HIV infection. Our patient clearly had an episode of APS that met the definition originally introduced by Harris et al. [8]. APS may be associated with either lupus anticoagulant positivity or the presence of aCL and/or antibodies against β2GP1 [9]. Our case is most unusual in that, during the first years, the only autoantibodies to phospholipid detected were those against prothrombin. Of interest was that the initial antibody response was directed against prothrombin, whereas later, after control of the HIV infection, the usual finding associated with lupus (i.e., detection of β2GP1) was then evident.

Recently, there has been much interest in the detection of anti-PT as a further means of detecting antiphospholipid antibody, which might be useful in patients who had previously been found to be antiphospholipid antibody negative by means of repeated testing with conventional methods. In 1995, Arvieux et al. [10] first designed an ELISA for the detection of anti-PT on γ-irradiated plates. They found a good correlation with lupus anticoagulant positivity, particularly in serum samples from autoimmune patients. In the following year, Puurunen et al. [11] reported that 50% of patients with SLE and thrombosis demonstrated anti-PT and that a strong correlation existed between anti-PT and anti-β2GP1. Anti-PT were usually accompanied by positivity for antibodies against β2GP and almost never seemed to occur alone. These results have subsequently been confirmed by some investigators [12] but not by others. For example, Swadzba et al. [13] found that IgG and IgM anti-PT did not associate significantly with thrombosis in patients with SLE or "lupus-like" disease. In recent reviews, Galli and Barbui [14] and Galli [15] also could not confirm any significant correlation between anti-PT and thrombosis in patients with both SLE and primary APS. However, Salcido-Ochoa et al. [16], in a recent study from Mexico involving patients with SLE and primary APS, found a higher frequency of anti-PT among patients with SLE and primary APS who had thrombosis, but no patients demonstrated anti-PT as the sole antiphospholipid antibody. Their conclusion was that the es-

timation and measurement of the anti-PT response did not provide additional clinical information.

Elevated levels of anti-PT have been reported in 2%–12% of HIV-infected patients, 6%–45% of patients with leprosy, and only 4% of patients with syphilis, as well as <10% of hepatitis C virus–positive serum specimens [17]. The occurrence of anti-PT and, indeed, APS in HIV-infected patients has been well reviewed. Loizou et al. [18] found a high prevalence of anti-PT in a selected group of 100 HIV-infected patients from South Africa. However, de Larranaga et al. [19] found a lower prevalence of anti-PT in 61 HIV-infected Argentine patients. The frequency of anti-PT, therefore, may be associated with ethnicity.

Lupus anticoagulants were first described in 44% of patients with AIDS and in 43% of asymptomatic HIV-infected individuals (in whom they could be transient) by Bloom et al. [20] in 1986. In 1997, Canoso et al. [21] reported aCL positivity in association with human T cell lymphotropic virus type 3 infection. In 1991, the association between aCL and HIV infection in men who have sex with men was reported [22], and several studies since then have confirmed these original findings. Coll et al. [23] evaluated 84 HIV-infected patients in the same year and found that 59.5% were IgG aCL positive. None of these patients had any thromboembolic phenomena, and no significant differences with respect to sex, risk factors, and stage of the disease were observed. Coll et al. [23] stated that aCL did not appear to be a prognostic marker in HIV-infected subjects but was rather indicative of a state of impaired humoral immunity. Falco et al. [24], in 1993, examined 39 HIV-positive serum samples and 20 aCL- and SLE-positive serum samples and found that, in the HIV-positive specimens, reduced aCL binding capacity was evident if the cofactor (i.e., β2GPI) was added. On the contrary, in SLE-positive serum samples, addition of the cofactor improved the binding capacity of aCL. Falco and colleagues concluded that aCL in patients with HIV infection appeared to have a different specificity than aCL found in patients with SLE. In 1995, Weiss et al. [25] found aCL in 47% of HIV-positive individuals, and other authors have confirmed this association [26–28].

SLE and HIV infection. The presence of SLE and HIV infection in the same individual is being increasingly reported as the incidence of HIV increases dramatically, particularly in Africa and Asia. SLE is not uncommon in the black population in South Africa and is associated with significant morbidity and mortality [29]. The coexistence of SLE and HIV infection in the same individual has, in some cases, previously been associated with remissions or amelioration of SLE symptoms occurring with advancing HIV infection during the pre-HAART era, whereas in other cases, it has been associated with "flares" in immune reconstitution, as was observed in patients during receipt of effective HAART [30]. A recent article from South Africa has drawn attention to the significant overlapping clinical and serological features between SLE and HIV infection, and the authors note that this overlap may lead to diagnostic difficulties and, indeed, to the institution of appropriate therapy in the black population of South Africa [31]. Arthralgias and frank arthritis, such as were seen in our patient, are only one such feature which may be seen in both conditions. Nonerosive symmetrical inflammatory arthritis occurs in both conditions, and a differential diagnosis may be impossible clinically. Polyclonal B cell activation is, of course, seen with HIV infection and is responsible for the wide range of autoantibodies observed in persons with this condition. The range even includes antibodies against double-stranded DNA, anti-Smith antibodies, as well as antiphospholipid antibodies. Additionally, autoimmune hemolytic anemia in association with positive results of the Coombs test is increasingly being recognized in HIV-infected patients [32]. Low complement levels are, however, not detected in patients with HIV infection.

The pathogenesis of SLE is still unknown. Several factors, however, have been observed, including a genetic predisposition, as well as environmental influences (including drugs and infectious agents). Endogenous retrovirus infections in humans are capable of integrating in key sites involved in immune regulation, generating an abnormal autoimmune response with the subsequent generation of antiretroviral antibodies that are cross-reactive with common nuclear antibodies [33]. For this reason, it is not uncommon that patients with SLE without previous exposure to retroviral infection may express antibodies against retroviral proteins, including gag, env, nef, and the p24 capsids of HIV-1 and human T cell lymphotropic virus type 3. Deas et al. [34] found that one-third of patients with SLE who had no previous exposure to HIV had a false-positive results of ELISA and Western blot for detection of HIV. Furthermore, some authors have suggested that these antibodies directed against HIV proteins may protect SLE subjects from exogenous infection [33].

Recently, Palacios et al. [30] described a 28-year-old white woman who received simultaneous diagnoses of SLE and HIV infection. This woman had malar rash, adenopathies, ascites, and mesangial glomerulonephritis in the presence of antinuclear antibodies, hypocomplementemia, anti-DNA antibodies, and positive serologic test results for HIV. Additionally, Palacios and colleagues described, in detail, 29 previously documented cases of the coexistence of these 2 disorders. They highlighted the fact that only 18 of 30 diagnoses labeled as SLE fulfilled the classification criteria of lupus. The remaining 12 patients had clinical features induced by HIV that simulate lupus. We are aware of only 5 new reports of patients with HIV infection and SLE that have been published since 2002 [31, 35–37].

Although these 2 diseases traditionally tend to affect different

population groups (homosexual transmission [in the case of HIV infection] and females of childbearing age [in the case of SLE]), with the increasing number of new cases in the heterosexual population and the clinical similarities (malar rash, oral ulcers, lymphadenopathies, fever, sicca symptoms, arthralgias, arthritis, and pancytopenia), it is mandatory to rule out HIV infection in black South African patients with SLE who seem to be pursuing an unsatisfactory course. Currently, during the HAART era, many questions are still unresolved in this field, including the real effect of immunosuppressive treatment for SLE on HIV infection and the effect of HIV treatment on SLE, as well as the pathogenic effects of a chronic viral infection during the course of SLE.

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References

1. Réveille JD. The changing spectrum of rheumatic disease in human immunodeficiency virus infection. Semin Arthritis Rheum **2000**; 30:147–66.
2. Cervera R, Asherson RA, Acevedo ML, et al. Antiphospholipid syndrome associated with infections: clinical and microbiological characteristics of 100 patients. Ann Rheum Dis **2004**; 63:1312–7.
3. Shen YM, Frenkel EP. Thrombosis and a hypercoagulable state in HIV-infected patients. Clin Appl Thromb Hemost **2004**; 10:277–80.
4. Saber AA, Aboolian A, LaRaja RD, Baron H, Hanna K. HIV/AIDS and the risk of deep vein thrombosis: a study of 45 patients with lower extremity involvement. Am Surg **2001**; 67:645–7.
5. Carr A, Brown D, Cooper DA. Portal vein thrombosis in patients receiving indinavir, an HIV protease inhibitor. AIDS **1997**; 11:1657–8.
6. Saif MW, Bona R, Greenberg B. AIDS and thrombosis: retrospective study of 131 HIV-infected patients. AIDS Patient Care STDS **2001**; 15:311–20.
7. Shahnaz S, Parikh G, Opran A. Antiphospholipid antibody syndrome manifesting as a deep venous thrombosis and pulmonary embolism in a patient with HIV. Am J Med Sci **2004**; 327:231–2.
8. Harris EN, Gharavi AE, Boey ML, et al. Anticardiolipin antibodies: detection by radioimmunoassay and association with thrombosis in systemic lupus erythematosus. Lancet **1983**; 2:1211–4.
9. Harris EN, Baguley E, Asherson RA, Hughes GRVH. Clinical and serological features of the "antiphospholipid syndrome" [abstract]. Br J Rheumatol **1987**; 26(Suppl 2):19.
10. Arvieux J, Darnige L, Reber G, Bensa JC, Colomb MG. Development of an ELISA for autoantibodies to prothrombin showing their prevalence in patients with lupus anticoagulants. Thromb Haemost **1995**; 74:1120–5.
11. Puurunen M, Vaarala O, Julkunen H, Aho K, Palosuo T. Antibodies to phospholipid–binding plasma proteins and occurrence of thrombosis in patients with systemic lupus erythematosus. Clin Immunol Immunopathol **1996**; 80:16–22.
12. Muñoz-Rodriguez FJ, Reverter JC, Font J, et al. Prevalence and clinical significance of antiprothrombin antibodies in patients with systemic lupus erythematosus or with primary antiphospholipid syndrome. Haematologica **2000**; 85:632–7.
13. Swadzba J, de Clerck I, Stevens WJ, et al. Anticardiolipin, anti–β2-glycoprotein 1, antiprothrombin antibodies and lupus anticoagulant in patients with systemic lupus erythematosus with a history of thrombosis. J Rheumatol **1997**; 24:1710–5.
14. Galli M, Barbui T. Antiprothrombin antibodies: detection and clinical significance in the antiphospholipid syndrome. Blood **1999**; 93:2149–57.
15. Galli M. Should we include anti-prothrombin antibodies in the screening of the antiphospholipid syndrome? J Autoimmun **2000**; 15:101–5.
16. Salcido–Ochoa F, Cabiedes J, Alarcon-Segovia D, Cabral AR. Antiprothrombin antibodies in patients with systemic lupus erythematosus or with primary antiphospholipid syndrome. J Clin Rheumatol **2002**; 8: 251–5.
17. von Landenberg P, Matthias T, Zaech J, et al. Antiprothrombin antibodies are associated with pregnancy loss in patients with the antiphospholipid syndrome. Am J Reprod Immunol **2003**; 49:51–6.
18. Loizou S, Singh S, Wypkema E, Asherson RA. Anticardiolipin antibodies, anti–β2-glycoprotein I and antiprothrombin antibodies in black South African with infectious diseases. Ann Rheum Dis **2003**; 62:1106–11.
19. de Larranaga GF, Forastiero RR, Carreras LO, Alonso BS. Different types of antiphospholipid antibodies in AIDS: a comparison with syphilis and the antiphospholipid syndrome. Thromb Res **1999**; 96:19–25.
20. Bloom EJ, Abrams DI, Rodgers G. Lupus anticoagulant in the acquired immunodeficiency syndrome. JAMA **1986**; 256:491–3.
21. Canoso RT, Zon LI, Groopman JE. Anticardiolipin antibodies associated with HTLV-III infection. Br J Haematol **1987**; 65:495–8.
22. Argov S, Shattner Y, Burstein R, Handzel ZT, Shoenfeld Y. Autoantibodies in male homosexuals and HIV infection. Immunol Lett **1991**; 30:31–6.
23. Coll J, Yazbeck H, Gutierrez J. Anticardiolipin antibodies in patients infected with human immunodeficiency virus type 1 [in Spanish]. Med Clin (Barc) **1993**; 100:357–8.
24. Falco M, Sorrenti A, Priori R, et al. Anticardiolipin antibodies in HIV infection are true antiphospholipids not associated with antiphospholipid syndrome. Ann Ital Med Int **1993**; 8:171–4.
25. Weiss L, You J-F, Giral P, Alhene-Gelas M, Senger D, Kazatchkine MD. Anticardiolipin antibodies are associated with anti-endothelial cell antibodies but not with anti–β2 glycoprotein 1 antibodies in HIV infection. Clin Immunol Immunopathol **1995**; 77:69–74.
26. Petrovas C, Vlachoyiannopolos PG, Kordossis T, Moutsopolos HM. Anti-phospholipid antibodies in HIV infection and SLE with or without antiphospholipid syndrome; comparisons of phospholipid specificity, avidity and reactivity with β2-GPI. J Autoimmun **1999**; 123:347–55.
27. Gonzales C, Leston A, Garcia-Berrocal B, et al. Antiphosphatidylserine antibodies in patients with autoimmune diseases and HIV-infected patients: effects of Tween 20 and relationship with antibodies to β2-glycoprotein I. J Clin Lab Anal **1999**; 13:59–64.
28. Silvestris F, Frassanito MA, Cafforio P, Potenza D, Di Loreto M,Tucci M. Antiphosphatidylserine antibodies in human immunodeficiency virus–1 patients correlate with evidence of T-cell apoptosis and mediate antibody-dependent cellular cytotoxicity. Blood **1996**; 87:5185–95.
29. McGill PE, Oyoo GO. Rheumatic disorders in sub-Saharan Africa. East Afr Med J **2002**; 79:214–6.
30. Palacios R, Santos J, Valdivieso P, Márquez M. Human immunodeficiency infection and systemic lupus eryhtematosus: an unusual case and a review of literature. Lupus **2002**; 11:60–3.
31. Gould T, Tikly M. Systemic lupus erythematosus in a patient with human immunodeficiency virus infection—challenges in diagnosis and management. Clin Rheumatol **2004**; 23:166–9.
32. Saif MW. HIV-associated autoimmune hemolytic anemia: an update. AIDS Patient Care STDS **2001**; 15:217–24.
33. Adelman MK, Marchalonis JJ. Endogenous retroviruses in systemic lupus erythematosus: candidate lupus viruses. Clin Immunol **2002**; 102:107–16.
34. Deas JE, Liu LG, Thompson JJ, et al. Reactivity of sera from systemic lupus erythematosus and Sjögren's syndrome patients with peptides derived from human immunodeficiency virus p24 capsid antigen. Clin Diagn Lab Immunol **1998**; 5:181–5.
35. Calza L, Manfredi R, Colangeli V, D'Antuono A, Passarini B, Chiodo F. Systemic and discoid lupus erythematosus in HIV-infected patients treated with highly active antiretroviral therapy. Int J STD AIDS **2003**; 14:356–9.
36. Wanchu A, Sud A, Singh S, Bambery P. Human immunodeficiency virus infection in a patient with systemic lupus erythematosus. J Assoc Physicians India **2003**; 51:1102–4.
37. Sommer S, Piyadigamage A, Goodfield MJ. Systemic lupus erythematosus or infection with HIV, or both? Clin Exp Dermatol **2004**; 29:393–5.

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AUTOINMUNIDAD E INFECCIÓN: HIPÓTESIS DEL MIMETISMO MOLECULAR

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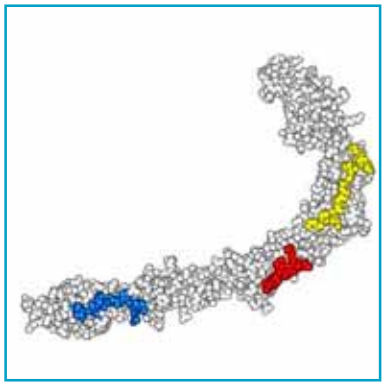

Contenido

El mimetismo molecular es uno de los mecanismos principales por el cual el síndrome antifosfolipídico (SAF) experimental puede ser desencadenado tras la presencia de patógenos. Al igual que en otras enfermedades autoinmunes, el concepto de mimetismo molecular permanece como una hipótesis viable para resolver algunas preguntas y enfoques, para descifrar y entender los mecanismos patogénicos implicados y para diseñar nuevas estrategias terapéuticas. Estudios en modelos experimentales de SAF y con péptidos sintéticos que comparten epítopes entre bacterias y virus con la mlécula β2GPI demuestran la existencia del mimetismo molecular entre los patógenos y los autoantígenos en el SAF. Nosotros especulamos que un antígeno con mimetismo molecular, similar en sólo un epítope, puede iniciar una respuesta inmunitaria mediante reacción cruzada hacia el epítope, que posteriormente dará como resultado el reconocimiento de numerosos epítopes de la β2GPI en el huésped. El mimetismo molecular podría ser uno de los mecanismos mediante los cuales se rompe la tolerancia y se desencadenan respuestas autoinmunes, si bien la sola presencia de los virus o las bacterias no necesariamente produce enfermedad. Un SAF "florido" sólo aparecerá si existe una determinada predisposición genética.

Introducción

Existe un consenso general en que las enfermedades autoinmunes tienen una etiología multifactorial y dependen tanto de factores genéticos como de factores ambientales. Los agentes bacterianos o los virus pueden inducir enfermedades autoinmunes por múltiples mecanismos (1-5). Así, proteínas de ciertos agentes infecciosos pueden actuar como activadores policlonales sobre un subtipo específico de linfocitos. Ciertos virus pueden, de manera selectiva, infectar o destruir a subtipos de linfocitos T y producir un desequilibrio en la respuesta autoinmune. En otras circunstancias, los agentes infecciosos pueden activar citocinas dependientes de la respuesta Th1, llevando a un aumento en la expresión de moléculas como las glicoproteínas del complejo mayor de histocompatibilidad (CMH), como también a una activación de moléculas co-estimuladoras. Se ha observado, asimismo, que ciertos agentes microbianos pueden codificar superantígenos que, de manera selectiva, activan subtipos de linfocitos T. Ciertos microorganismos, a su vez, son capaces de activar la liberación de citocinas y quimocinas, que actúan como factores de crecimiento, diferenciación y quimiotácticos para diferentes poblaciones Th, regulando la expresión de moléculas del CMH de clase I y clase II (1-5).

El sistema de inmunidad normal tolera a una serie de moléculas de las cuales está conformado el organismo. Sin embargo, entre los principales antígenos reconocidos en las infecciones bacterianas, víricas y parasitarias existen proteínas, con una secuencia o una conformación similar a las moléculas del huésped. A esta respuesta anormal a dichos antígenos se le conoce como *mimetismo molecular*. La similitud antigénica a las secuencias de cadenas de aminoácidos o a la conformación estructural entre los antígenos de los agentes infecciosos y los tejidos del huésped puede activar una respuesta contra las regiones específicas que se comparten. Como resultado, se pierde la autotolerancia a los antígenos propios y comienza una respuesta inmunológica patógeno-específica que genera una reacción cruzada contra las estructuras del huésped, causando daño tisular y enfermedad. El papel del mimetismo molecular en la patogenia de las enfermedades autoinmunes se ha demostrado recientemente en modelos animales, como la encefalomielitis alérgica, la miocarditis experimental y la uveitis-queratitis experimental autoinmune (5-10). Recientemente, dos grupos de investigadores encontraron mimetismo molecular entre patógenos comunes y la •2-glicoproteína-I (•2GPI), la cual es una de las principales moléculas implicadas en la patogenia del síndrome antifosfolipídico (SAF) (11-14).

Síndrome Antifosfolipídico (SAF)

El síndrome antifosfolipídico se caracteriza por la presencia de anticuerpos antifosfolipídicos (AAF), como los anticuerpos anticardiolipina (AAC), que se unen a moléculas de fosfolípidos principalmente a través de la ß2GPI, y el anticoagulante lúpico (AL), que están relacionados con el desarrollo de fenómenos tromboembólicos, pérdidas fetales recurrentes, trombocitopenia y alteraciones neurológicas y cardiacas, entre otras manifestaciones clínicas (15-21).

La molécula humana de la •2GPI es una glicoproteína de membrana de adhesión, de 326 aminoácidos, presente en el plasma sanguíneo a concentraciones entre 150 a 300 ug/ml (22,23). La •2GPI exhibe varias propiedades *in vitro* que la definen como un anticoagulante (p.ej. inhibición de la actividad de la protrombinasa, agregación plaquetaria inducida por ADP y producción de factor IX plaquetario) (24,25). Participa además en la depuración de cuerpos apoptóticos de la circulación (26). Se ha encontrado que tiene propiedades inmunogénicas *in vivo*. La inmunización de ratones BALB/c, PL/J o conejos de Nueva Zelanda blancos con •2GPI genera anticuerpos anti-•2 GPI (27-30). Los ratones inmunizados con •2GPI desarrollan títulos elevados de AAC, asociados con un alto porcentaje de reabsorciones fetales (el equivalente a pérdidas fetales en el SAF humano), trombocitopenia y prolongación del tiempo parcial de tromboplastina activado (TTPA), lo cual indica la presencia de AL (29). Se ha observado además una aceleración de las manifestaciones del SAF en ratones MRL/lpr (un modelo murino de SAF con base genética) inmunizados con •2GPI (31). Asimismo, se ha prevenido la aparición de SAF en ratones alimentados por vía oral con •2GPI en los cuales se indujo tolerancia (32).

Los anticuerpos anti- •2GPI ejercen un efecto patogénico directo al interferir con las reacciones homeostáticas que ocurren en la superficie de los monocitos, las plaquetas y las células endoteliales vasculares (33-35). Se ha encontrado que la activación de los monocitos por los anticuepos anti-•2GPI genera la liberación del factor tisular (34-35) y la activación de las células endoteliales, las cuales inducen la expresión de moléculas de adhesión, como la E-selectina, el ICAM-I, el VCAM-I y el NFkB (37-39). La transferencia pasiva a ratones previamente no inmunizados de estos anticuerpos o de anticuerpos contra •2GPI por péptidos sintéticos homólogos a bacterias comunes da como resultado la inducción de un modelo experimental de SAF (38,42,43). El intercambio entre las cadenas ligeras y pesadas de los anticuerpos patogénicos anti- •2GPI y la cadena sencilla Fv de los anticuerpos no patogénicos ha mostrado que el segmento patogénico de la molécula de anti- ß2GPI se encuentra localizado en el CDR3 de la cadena pesada de la inmunoglobulina (44). Nuestro grupo (38) y otros grupos de investigadores (45-53) han descrito que los epítopes diana para la unión de los anti- •2GPI a la molécula •2GPI están diseminados en diferentes lugares a lo largo de los 5 dominios de la molécula. Varios pacientes con SAF presentan un panel ampliamente diferenciado contra anticuerpos anti-•2GPI dirigidos contra los diferentes epítopes (38,54).

Origen de los anticuerpos anti-•2GPI en el plasma

La molécula •2GPI y la cardiolipina son moléculas ubicuas. Se han propuesto varias vías para explicar la genera-

ción de anticuerpos patógenos contra ellas. Se ha sugerido que el epítope críptico de la •2GPI está expuesto a la unión de superficies oxidadas (55). Otros han propuesto que los epítopes son reconocidos por muchos AAF que están adheridos a fosfolípidos oxidados y asociados a proteínas, como la molécula de la •2GPI (56). La forma oxidada de la •2GPI lleva un cambio conformacional y presenta nuevos epítopes, los cuales inducen anticuerpos anti-•2GPI (56,57). La presentación de las moléculas de •2GPI a las células apoptóticas mediante la unión a la fosfatidilserina puede inducir linfocitos B con receptores Ig para células apoptóticas y DNA, los cuales son seleccionados positivamente y pueden generar AAF en condiciones apropiadas (58,61). Durante los últimos años, varias bacterias y virus ubicuos han sido analizados para ver su capacidad de generar SAF experimental (11,14).

Infección y anticuerpos antifosfolipídicos

Muchas infecciones pueden acompañarse por la elevación de AAF y en algunas de ellas dicha elevación se acompaña de manifestaciones clínicas del SAF. Varias revisiones de este importante tema han sido realizadas en profundidad recientemente (62-65). Las infecciones cutáneas (18%), la infección por el virus de la inmunodeficiencia humana (VIH) (17%), las neumonías (14%), las infecciones por virus de la hepatitis C (VHC) (13%) y las infecciones urinarias (10%) constituyen las infecciones más comúnmente encontradas como factores desencadenantes en una reciente revisión (66). En 9 casos, más de un agente u órgano fueron identificados como fuentes de la infección. Otras infecciones menos frecuentes asociadas fueron las producidas por micoplasma (3 casos), tuberculosis pulmonar (2 casos), malaria (2 casos), P. carinii y leptospirosis (1 caso cada una). No solamente se producen AAC de isotipo IgM sino también se han encontrado elevaciones de IgG en algunos sueros.

SAF catastrófico e infecciones

Este subtipo de SAF, inusual y potencialmente letal, fue por primera vez descrito en 1992 (67). Desde entonces, más de 150 pacientes (68,69) han sido ampliamente analizados y documentados en publicaciones importantes, aunque actualmente más de 200 casos individuales han sido descritos (70) y su fisiopatología ha sido revisada en detalle (71). Los factores desencadenantes son cada vez más reconocidos y han sido descritos en el 51% de los casos del análisis más reciente (70). Entre estos se incluyen la cirugía (mayor o menor), la suspensión de la anticoagulación, diversos carcinomas y el más importante y común de ellos, las infecciones, las cuales han sido identificadas en el 24% de los pacientes. Diversas infecciones precediendo la aparición del SAF catastrófico (SAFC) fueron descritas en 8 pacientes por Rojas-Rodríguez y cols (72) mientras que Undas y cols (73) describieron 3 episodios de SAFC (uno de ellos con SAFC "recurrente") que fueron precedidos por una infección. La revisión más reciente de infecciones y AAF (65) mostró que 40 de los 100 pacientes (40%) se manifestaron como SAFC, el cual parece ser tan frecuente como el SAF "clásico" cuando el desencadenante es una infección. Todo esto teniendo en cuenta el escaso número de casos descritos hasta la fecha de SAFC, en comparación con los miles de casos descritos de SAF "clásico". Estas infecciones incluyen las del aparato respiratorio (10%), piel (4%), tracto urinario (4%), tubo digestivo (2%), sepsis (1%) y otras (3%). En el último grupo, se encontró un paciente que desarrolló SAFC después de una infección por fiebre tifoidea (74). Otro caso similar de oclusión de grandes vasos tras una fiebre tifoidea ha sido recientemente publicado (75), pero, aunque este paciente fue catalogado como un SAFC, no hubo evidencia de trombosis de pequeños vasos, lo cual es fundamental para el diagnóstico de SAFC, de acuerdo a las guías recientemente publicadas (76). Se han descrito ocasionalmente casos de SAFC tras diversas otras infecciones, como son dos casos de malaria (77), un caso de fiebre dengue en Brasil (78) y un caso tras la vacunación contra la encefalitis japonesa B en un paciente israelí (79). También se ha descrito la resolución del SAFC tras la amputación de una extremidad gangrenosa en dos pacientes (80). El "mimetismo molecular" se ha propuesto como uno de los principales mecanismos para el desarrollo del SAFC después de una infección (81) aunque también participan otros mecanismos.

Tabla 1. Manifestacions del SAF asociadas con infecciones víricas.

Agente infeccioso	AAC	•2GPI	Manifestaciones del SAF
Hepatitis C	IgG	+	Trombosis, infarto cerebral
VEB	IgG, IgM	+	*EP, trombosis,
Varicela	IgG, IgM	-	EP, trombosis
Parvovirus B19	IgG	+	Trombosis
CMV	IgG, IgM	+	Trombosis
HTLV-1	IgA	-	**ND
VIH	IgG, IgM, IgA	+	Ulceras en piernas, EP, ***EV, Trombosis arterial y venosa, vasculitis, livedo reticularis
Adenovirus	IgG	+	Trombocitopenia

* EP-embolismo pulmonar ** ND- no detectado *** EV – Embolismo venoso

Etiología infecciosa de los anticuerpos anti-• 2GPI

Mimetismo molecular entre patógenos comunes y epítopes de la • 2GPI como posible causa de la aparción de anticuerpos anti-• 2GPI

La hipótesis del mimetismo molecular entre el agente patógeno y la molécula de • 2GPI como causa del SAF se basa en: a) la correlación entre el desarrollo de manifestaciones del SAF y el antecendente de episodios infecciosos en humanos; b) la fuerte similitud entre péptidos de la • 2GPI (epítopes diana para anticuerpos anti-• 2GPI) y proteínas de diferentes patógenos comunes (Tabla 3).

Nuestro grupo ha identificado varios péptidos sintéticos como epítopes diana para los anticuerpos anti-• 2GPI mediante la utilización de anticuerpos monoclonales humanos anti-• 2GPI obtenidos de pacientes con SAF. Estos péptidos de la • 2GPI fueron localizados en el dominio I-II (mimotope), dominio III y dominio IV (secuencias lineales) (Figura 1). Los tres péptidos sintéticos inhiben la activación de las células endoteliales *in-vitro* y la inducción de SAF experimental en ratones previamente no inmunizados y neutralizan los anticuerpos anti-• 2GPI patógenos (38). La prevalencia de los anticuerpos anti péptido A-C circulantes en el suero de 295 pacientes varía entre 18% hasta 47,5% (54). Empleando la base de datos de las proteínas, nuestro grupo encontró similitudes entre nuestros péptidos y los de otras bacterias y virus comunes, levaduras y toxina tetánica (Tabla 3). Con el fin de comprobar la participación del mimetismo molecular entre el patógeno y la molécula de • 2GPI como causa del SAF experimental, vacunamos a ratones previamente no expuestos con agentes microbianos patógenos, los cuales compartían homología estructural con el hexapéptido TLRVYK. Se encontraron anticuerpos IgG murinos especificos anti-TLRVYK utilizando el péptido TLRVYK purificado de un ratón inmunizado y posteriormente infundidos e.v. a ratones previamente no inmunizados en el día 0 del embarazo. Después de la inmunización, se observaron diferentes niveles de anticuerpos anti-• 2GPI y los más elevados fueron encontrados en aquellos ratones inmunizados con *Haemophilus influenzae*, *Neisseria gonorrhoeae* o toxoide tetánico. Los ratones infundidos con estos anticuerpos anti-ß2GPI tuvieron tasas similares de trombocitopenia, TPTA prolongado y pérdidas fetales que el grupo control de ratones inmunizados con anticuerpos anti-• 2GPI monoclonales (11). Más aún, nuestro estudio estableció un mecanismo de mimetismo molecular en SAF experimental demostrando que la estructura • 2GPI homóloga a la bacteriana es capaz de generar anticuerpos anti- • 2GPI patógenos junto con manifestaciones de SAF (11).

TABLA 2. Prevalencia de AAC en diversas infecciones.

Infección	Prevalencia AAC (%)	Isotipo
Tifus	20	-
Lepra	33-67	IgG, IgM, IgA
Tuberculosis	27-53	IgG, IgM
Endocarditis bacteriana	5-44	IgG, IgM
Helicobacter pylori	*ND	IgG, IgM
Mycoplasma pneumonia	20-53	IgG, IgM, IgA
S. aureus	43	IgG, IgM, IgA
Streptoccocus	80	IgG, IgM, IgA
Streptoccocus pyogenus	0-80	IgG, IgM
Salmonella	60	IgG, IgM, IgA
E. Coli	67	IgG, IgM, IgA
Ornitosis	33	IgG, IgM, IgA
Coxiella butneti	42-84	IgG, IgM
Leptospirosis	50	IgG
Borrelia burgdorferi	14-41	IgG, IgM
Saccharomyces cervevisiae	ND	IgG
Malaria	30	IgG, IgM
Kala-azar	ND	IgG

De manera paralela, Gharavi y cols (82,83) indujeron anticuerpos anti-• 2GPI circulantes en ratones previamente no inmunizados mediante la vacunación con péptidos sintéticos conjugados para BSA, los cuales comparten algunas similitudes con la proteína fijadora para DNA tipo 2 del adenovirus humano 72kd, con el CMV, con el HCMVA y con el *Bacillus subtilis*.

Nosotros creemos que las partículas patógenas son digeridas y presentadas a los macrófagos, a las células dendríticas o a los linfocitos B. Estas partículas patógenas son presentadas a los linfocitos T, lo cual, junto con una apropiada presentación del HLA y una activación en la expresión de la cascada de citocinas Th1/Th2, lleva a la generación de células plasmáticas que secretan anticuerpos anti-• 2GPI dirigidos contra partículas patógenas, que comparten estructuras homólogas (mimetismo molecular) con la molécula • 2GPI (Figura 3). El hecho de que un individuo desarrolle un SAF dependerá principalmente de su predisposición genética.

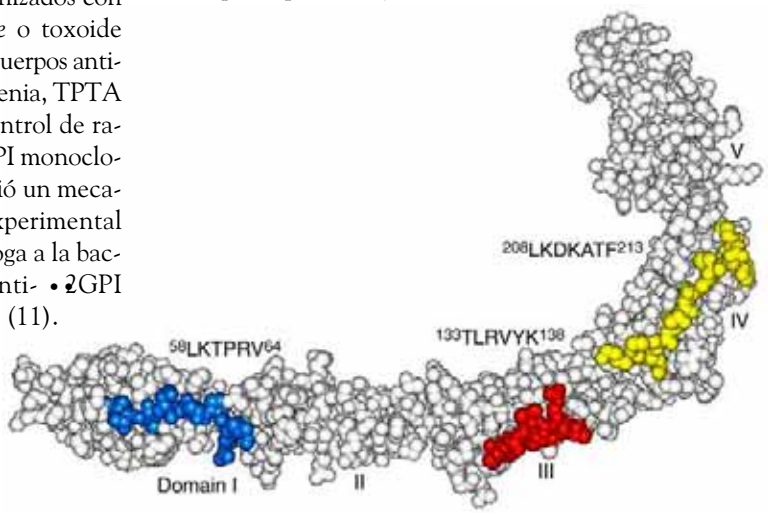

FIGURA 1.
Localización de los péptidos de la • 2GPI.

TABLA 3. AAF detectados en diversas infecciones y homologías peptídicas con la β2GPI.

	Infecciones asociadas con AAF	*TLRVYK (38)	LKTPRV (38)	KDKATF (38)	GDKVSFF (49)	GRTCPKPDDLP (53)
Víricas						
CMV	+		+		+	
VEB	+	+				
VIH	+	**+	+			
Hepatitis C	+					
Parvovirus B19	+					
Adenovirus	+		+			
Varicela	+					
Vacuna	+	+				
Parotiditis	+					
Rubeola	+					
HTLV-1	+					
herpesvirus	-				+	
Bacterianas						
Lepra	+					
Tuberculosis	+	+	+			
M pneumoniae, M penetrans	+					
Salmonella	+	*+ typhi*				
Staphylococci	+	+	+	+		
Streptococci	+	*+pyogenes*	*+pyogenes*	+		
Chlamydia	-			+	+	
Trypanosome brucei rhodesiense	-	+				
Coxiella burnetii	+		+	+		
Porphyromonas gingivalis	-	+				
Helicobacter pylori	+	+	+			+3
Haemophilus influenzae	-	+		+		
Neisseria gonorrhoeae	-	+				
Neisseria meningitidis	-		+			
Shigela dysenteriae	-	+				
Pseudomonas aeroginosa	-		+			
Yersinia pseudotuberculosis	-		+			
Klebsiella pneumoniae	+			+		
Campylobacter jejuni	-	+		+		
E.Coli	-	+	+	+		
Brucella melitenensis	-			+		
Spiroquetas						
Treponema						
Palidum (Sífilis)						
Leptospira	+					
Borrelia	+	+	+			
Burgdorferi						
Parásitos						
Kala azar	+					
Schistosoma mansoni	-		+			
Toxoplasmosis	+					
Hongos						
Saccharomyces cervevisiae (Crohn)	+	+	+	+		
Candida albicans	-	+				
Streptomyces lividans	-		+			
mycoplasma	+		+ *pulmonis genitalium*	*+pneumonia capricolum genitalium pulmonis*		

* Homologías entre los péptidos de la β2GPI y diferentes agents patógenos detectadas mediante la base de datos suiza (actualizada en abril de 2003).
** Dos estructuras compartidas.

Lecciones obtenidas de la base de datos suiza sobre las correlaciones entre varios patógenos comunes, la estructura de la •2GPI y los péptidos relacionados con la •2GPI

La Tabla 3 resume las similitudes lineales entre diversos péptidos de la molécula •2GPI y patógenos comunes, reconocidas utilizando la base de datos proteica suiza. Previamente, nosotros hemos demostrado mimetismo molecular entre patógenos comunes y péptidos relacionados con la •2GPI, en los cuales se encontraron similitudes biológicas funcionales en 2 de los 7 complejos •2GPI/patógenos y los anticuerpos para estos epítopes compartidos que inducían SAF experimental. Por esto, a) debe considerarse como limitación la probabilidad de un emparejamiento incorrecto; b) debe tenerse en cuenta la probabilidad de que muchas estructuras conformacionales son compartidas entre la molécula •2GPI y patógenos comunes (posteriormente se dará un ejemplo para el virus de la vacuna, el cual comparte similitudes con estructuras terciarias con la molécula •2GPI, pero no comparte similitudes con la secuencia de aminoácidos) (Figura 2).

Helicobacter pylori, anticuerpos anti-•2GPI y SAF

El *Helicobacter pylori* (*H. Pylori*) es uno de los patógenos bacterianos más comunes en el humano, que coloniza la mucosa gástrica y donde parece que persiste a lo largo de toda la vida del paciente, a menos que sea tratado. La colonización induce inflamación gástrica crónica, lo cual puede progresar a una variedad de enfermedades que van desde una gastritis superficial y una úlcera péptica a un cáncer gástrico o a un linfoma de mucosa. Se ha propuesto que las características específicas de cada cepa son las responsables de la capacidad de cada organismo para causar diferentes enfermedades, o incluso para influir de manera positiva en la capacidad para la cepa de infectar el huésped de manera crónica a lo largo de la vida (84). Recientemente se describió la desaparición de los AAF tras la erradicación del *H. pylori* (85).

La diferente información acumulada demuestra que el *H. pylori* tiene diversos efectos clínicos: a) La infección por el *H. pylori* puede afectar el crecimiento fetal intrauterino, aumentando el riesgo de desarrollar trastornos reproductivos (87); b) los ratones infectados por *H. pylori* tienen un nivel elevado de embolización de plaquetas tras un daño en las arteriolas (88); c) la infección por el *H. pylori* se ha sugerido como un factor de riesgo para la isquemia cerebral (89) y como factor de riesgo para enfermedad coronaria (90). En todos estos casos, la correlación entre anticuerpos anti-•2GPI o péptidos relacionados con la •2GPI deberían ser analizados. El cribado en 50 pacientes con infección por *H. pylori* para la presencia de anticuerpos anti-•2GPI mostró una prevalencia del 33,3% (91).

Basados en el gran número de genes relacionados con la secuencia que codifica proteínas de membrana y la presencia de trayectos homopoliméricos y de repetición de dinucleótidos en las secuencias codificadas, el *H. Pylori*, como otros patógenos de la mucosa, presentan mecanismos para la variación antigénica y la evolución adaptativa. Asimismo, el *H. pylori* tiene pocas redes de regulación y un limitado repertorio metabólico. Su supervivencia, en

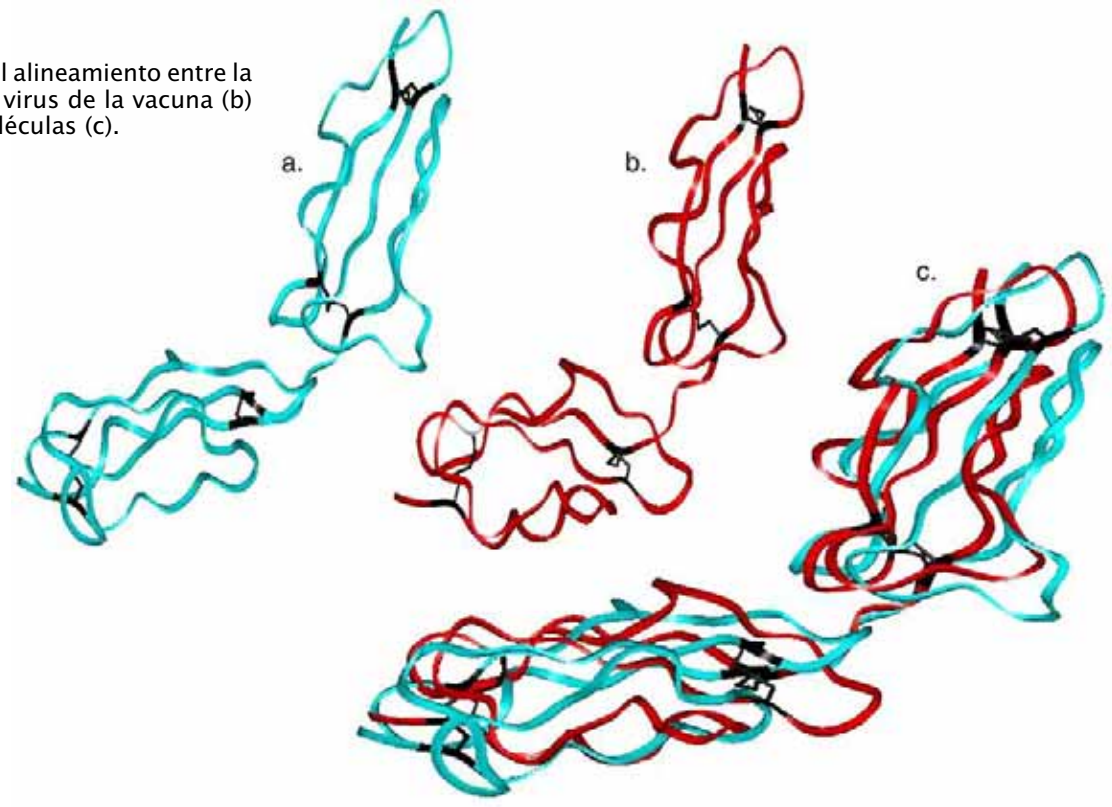

FIGURA 2.
Diagrama del alineamiento entre la •2GPI (a), el virus de la vacuna (b) y ambas moléculas (c).

condiciones ácidas, depende en parte de su capacidad de establecer un potencial interno de membrana a un pH bajo (92). Utilizando la base de datos proteica suiza, nuestro grupo fue capaz de detectar similitudes (mis 1-2) entre los epítopes diana de los péptidos de • 2GPI y estructuras de *H. pylori* (Tabla 3), como, por ejemplo, la proteína Q9zmk9, una proteína de reparación del DNA homóloga al radA, que juega un papel en la reparación endógena al daño por alquilación, la proteína de división celular ftsA-Q9zmk3, que está involucrada en el crecimiento filamentoso anómalo (por similitud), el antígeno inmunodominante asociado con la citotoxicidad –P55980, que es necesario para la transcripción, el plegamiento, la exportación y la función de citotoxinas, la proteína 2 asociada al gancho flagelar (HAP2) –P96786, un factor esencial en la estructura y movilidad flagelar, la Q9zmz4 y la subunidad alfa ureasa P14916 (urea amino hidrolasa).

Streptococcus pyogenes, anti-• 2GPI y SAF

La fiebre reumática (FR) y la posterior enfermedad cardiaca reumática son enfermedades del tejido conjuntivo relativamente comunes causadas por el *Streptoccocus pyogenes*. Se ha descrito el mimetismo molecular, principalmente entre la proteína M y las propias estructuras, como el principal mecanismo para el desarrollo de FR aguda después de una faringitis estreptocócica. La proteína M y otros antígenos aún no muy bien definidos de la célula bacteriana han sido relacionados con una reacción cruzada con proteínas humanas que tienen estructuras enrolladas, como la miosina, la tropomiosina y las proteínas valvulares. Además de la aparente reacción cruzada entre los anticuerpos anti-steptoccocus, la inmunología de la FR es complicada por los anticuerpos cardiacos bajo la forma de inmunoglobulinas que se unen al miocardio y endocardio, como también por otros anticuerpos circulantes en el suero que se une contra estructuras cardiacas. En la FR se ha decrito una amplia variedad de respuestas por anticuerpos. Dicha respuesta puede estar relacionada con la hiperactivación de los linfocitos B o con las reacciones cruzadas dependientes de antígenos (93-95).

La FR y el SAF comparten ciertas similitudes clínicas como son el compromiso del sistema nervioso central y del corazón. Nosotros creemos que puede ser consecuencia de una reacción cruzada entre la proteína M y la • 2GPI. Los péptidos TLRVYK y LKTPRV relacionados con la • 2GPI comparten similitudes con la proteína M *del Streptococcus pyogenes*. El péptido TLRVYK relacionado con la • 2GPI inhibe la unión de los anticuerpos anti proteína M de los pacientes con FR en un 37%. Los anticuerpos anti-• 2GPI pueden ser inhibidos por la proteina M que se une a la • 2GPI en un 23%.

Borrelia burgdorferi, anti-• 2GPI y SAF

La espiroqueta *Borrelia burgdorferi* es la causante de la enfermedad de Lyme. Un subgrupo de pacientes (50%) con neuroborreliosis muestran reactividad IgG para cardiolipina en fase sólida ELISA (96,97). Ya que la prueba fue realizada en 1987 con el suero como bloqueador, probablemente la reacción es dependiente de • 2GPI.

Los péptidos TLRVYK y LKTPRV relacionados con la • 2GPI comparten similitudes con la *Borrelia burgdorferi*, la glicerol cinasa-Q51257 y la proteína glutamato-metil-esterasa-051376.

Saccharomyces cerevisiae, anti-• 2GPI y SAF

Los anticuerpos circulantes anti-*Saccharomyces cerevisiae* IgA e IgG (ASCA) son unos de los marcadores principales de la enfermedad de Crohn (98). Dentro de las respuestas serológicas que se encuentran en esta enfermedad están los anticuerpos anti *Saccharomyces cerevisiae*, anti-micobacterias, anti-bacteroides, anti-listeria y anti-*E. coli*. Muchos de estos microorganismos participan en la patogenia de la enfermedad de Crohn. La oligomanosa, la paratuberculosis p35 y los antígenos p36 son epítopes del Saccharomyces cerevisiae demostrados hasta en un 60 a un 70% de los pacientes con enferemedad de Crohn. Los pacientes con enfermedad inflamatoria intestinal tienen niveles circulantes elevados de AAC y anti-• 2GPI (99-101) y, aunque se han descrito casos de trombosis asociados a la elevación de anti-• 2GPI en la enfermedad de Crohn (99-101), su papel patogénico aún no está claramente establecido.

La asociación con los ASCA ha sido descrita también en otra enfermedad autoinmune, como la enfermedad de Behçet, aunque sin ninguna relevancia clínica (102). La trombosis, habitualmente venosa, ocurre entre un 10 a un 25% de los pacientes con enfermedad de Behçet, aunque su patogenia aún se desconoce (101). Se han descrito asociaciones entre el SAF y la enfermedad de Behçet, incluyendo un caso de trombosis total de la vena cava (105). Famularo y cols. (106) describieron un caso de un paciente con una recaída potencialmente letal de una enfermedad de Behçet asociada a un SAFC. El paciente experimentó en un período corto de tiempo un infarto agudo de miocardio recurrente, múltiples trombosis venosas, uveítis y eritema nudoso. La investigación de factores trombofílicos mostró positividad para AL, cumpliendo así criterios para SAF (106). La reactividad cruzada funcional entre los ASCA, los anti-• 2GPI y los péptidos relacionados con anti-• 2GPI debe ser analizada en un futuro.

Finalmente, utilizando la base de datos de proteínas suiza, se han encontrado varias similitudes entre los péptidos relacionados con la • 2GPI y el *Saccharomyces cerevisiae* (Tabla 3).

Actividad dual de los anticuerpos anti-• 2GPI frente a las infecciones

Un amplio rango de interacciones proteína-proteína específicas en la superficie celular y en el suero son mediadas por unos dominios proteicos versátiles funcionalmente con 60 residuos de aminoácidos, llamados proteínas de control del complemento (PCC), los cuales se caracterizan por poseer una única secuencia consensuada. Entre los ligandos, podemos encontrar la molécula de • 2GPI, la

heparina, el virus del Epstein Barr (VEB), el virus del sarampión, el enterovirus 70, el ecovirus y proteínas bacterianas como la proteína M del grupo del *Staphilococcus pyogenes* y la molécula de adhesión de *E. coli*. Los módulos PCC han sido identificados hasta ahora en 50 proteínas plasmáticas diferentes de mamíferos, en la superficie de muchos tipos celulares, en la matriz acrosomal del espermatozoide, la retina, el cerebro y otras (107).

Utilizando la base de datos proteica suiza, encontramos un alineamiento fuertemente significativo entre la molécula de •2GPI y varias secuencias relevantes o moléculas de control de patógenos. Aquí presentamos algunos ejemplos y discutimos la relevancia funcional de los anticuerpos anti-•2GPI como autoanticuerpos naturales o como anticuerpos patógenos.

Virus de la vacuna

El virus de la vacuna y la gammaglobulina anti-vacuna son utilizados para la vacunación contra la viruela. Aunque esta enfermedad actualmente está erradicada en la mayoría de países, algunas muertes atribuidas a la vacunación contra la viruela fueron debidas a la transmisión del virus de la vacuna (108). Los dominios 3-4 de la molécula b2GPI comparten estructuras terciarias similares a la PCC del virus de la vacuna (VCP) (Q89859) (Figura 3). Esta proteína de 253 residuos es un regulador de la activación del complemento y su papel es defender al virus contra el ataque del sistema de complemento del huésped. La •2GPI compite junto a esta proteína de residuo VCP por su receptor de reconocimiento, facilitando la activación del complemento como respuesta al virus. Los anticuerpos anti-•2GPI pueden actuar sobre los VCP mediante la neutralización del virus inhabilitando la activación del complemento.

Interrelación entre el VEB, la •2GPI y los anticuerpos anti-•2GPI

El CR2 es el receptor para el C3d, el fragmento de 33kd del tercer componente del complemento. El CR2 es también el receptor del VEB (EBV/C3d, CD 21). EL CR2 se une a sus dos ligandos extracelulares, el C3d y la glicoproteína de la cápside del VEB gp350/220 a través de 2 sitios diferentes de unión. El CR2 permite al C3d y al VEB inducir proliferación (109). Teóricamente, se pueden prever diferentes escenarios con respecto a las interrelaciones VEB-•2GPI y los anticuerpos anti-•2GPI: Los anticuerpos anti-•2GPI pueden generarse por un mecanismo de mimetismo molecular como está descrito en la Figura 2. Estos anticuerpos pueden neutralizar el VEB o el CR2 si reconocen un epítope compartido y así prevenir la mononucleosis infecciosa. Asimismo, pueden aumentar la gravedad de la enfermedad si los anticuerpos anti-•2GPI reconocen diferentes epítopes en el VEB y en el CR2. La presencia de los anticuerpos anti-•2GPI circulante ha sido descrita en pacientes con mononucleosis infecciosa sin correlación con la actividad de la enferme-

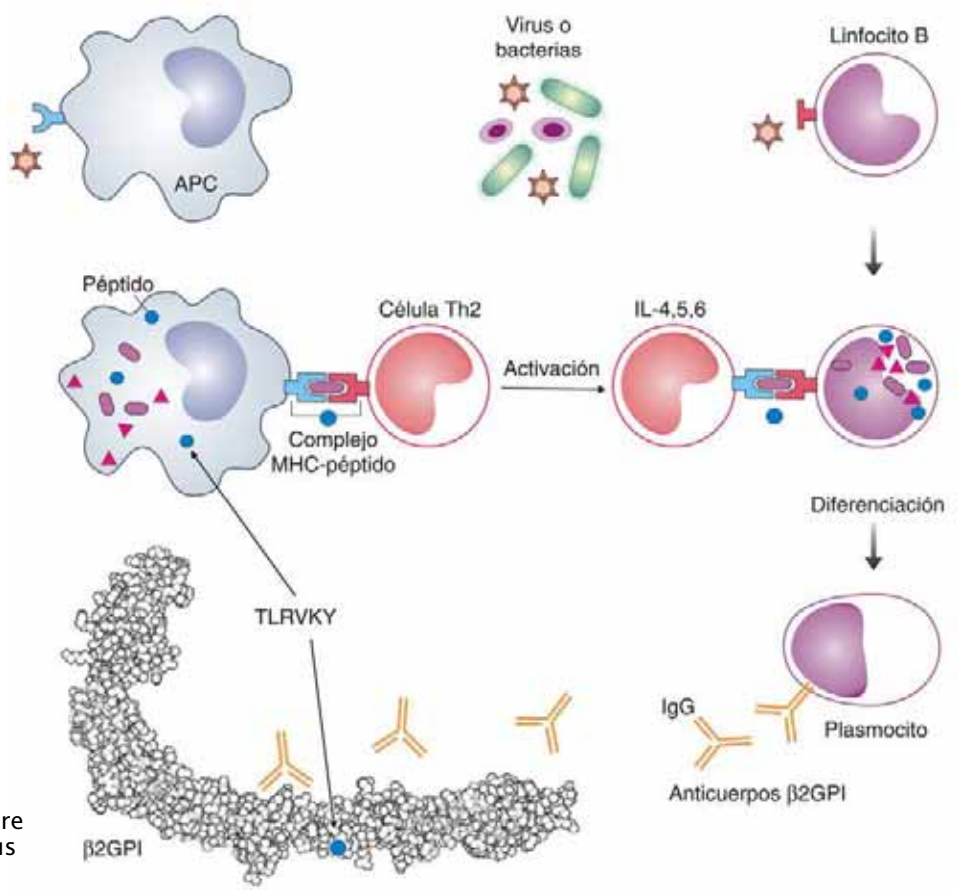

FIGURA 3.
Mimetismo molecular entre la •2GPI y bacterias y virus comunes.

dad (110). Sin embargo, un amplio rango de poblaciones han sido expuestas al VEB sin tener anticuerpos anti-• 2GPI ni mononucleosis infecciosa.

Compromiso de los anticuerpos anti-• 2GPI en el control de la activación del complemento

Como se discutió previamente, la exposición a un patógeno puede inducir la generación de anticuerpos anti-b2GPI patogénicos contra los epítopes compartidos entre el patógeno relevante y la molécula • 2GPI. Teniendo un alto alineamiento entre la • 2GPI y algunas PCC, los anticuerpos anti-• 2GPI pueden interferir con la activación del complemento. Uno de los mecanismos propuestos para el SAFC es el aumento de la activación del complemento (114,115). Además, muchos estudios han mostrado que la activación no controlada del complemento en la placenta lleva a la muerte fetal *in utero*. La inhibición *in-vivo* de la cascada del complemento previene las pérdidas fetales inducidas por anticuerpos anti-• 2GPI, utilizando el inhibidor C3 de la convertasa CR-1 relacionada con el gen/proteína (Crry)-Ig (116). Teóricamente, la • 2GPI puede tener mimetismo con el CR1; así, los anticuerpos anti-• 2GPI pueden proteger al inhibidor del complemento y aumentar la activación de éste.

Anticuerpos anti-• 2GPI y el cofactor de la proteína de membrana CD46

Un fuerte alineamiento entre la • 2GPI y una estructura terciaria del cofactor de la proteína de membrana (CPM) CD 46 (5e-18) fue detectado en la base de datos. El CPM fue previamente identificado como la célula receptora del huésped para las cepas del virus del sarampión del laboratorio Edmonston. La CD46 es una molécula ubicua, miembro de la familia de las proteínas protectoras reguladoras de la activación del complemento e interfiere con la formación del complejo de ataque del complemento en la membrana de las células normales y previene la lisis de las células no reguladas del huésped (117). Por esto, la CD46 juega un papel importante en la protección del tejido no infectado contra el daño mediado por el complemento. Es un tipo de glucoproteína de membraba con diferentes isoformas de 57-67 masas moleculares. Así, los anticuerpos anti-• 2GPI neutralizarán esta proteína y permitirán el aumento en la activación del complemento y la patogenia de la enfermedad. Asimismo, la CD46 se une por medio de una interacción hidrofóbica con la proteína H del sarampión. Mediante un posible mimetismo molecular con la molécula CD46, la • 2GPI podría fijar la proteína H del sarampión y proteger la célula normal.

Relación con la inmunidad innata

Los receptores "*toll-like*" (TLR) son responsables de la respuesta protectora inmediata contra patógenos (inmunidad innata) e instruyen la respuesta inmune adquirida (118). Recientemente, se ha postulado la existencia de un punto de unión entre los sistemas de inmunidad innata y adquirida en el desarrollo de enfermedades autoinmunes sistémicas como el lupus eritematoso sistémico (119-121). Los linfocitos B desarrollan un papel esencial en la respuesta inmune adquirida y en la innata. Se han encontrado complejos de cromatina-IgG para activar los linfocitos B mediante un convenio dual de IgM con los TLR (122), lo cual es conocido para detectar el DNA CpG bacteriano (123). Estudios recientes han revelado estructuras moleculares comunes de los microorganismos, como los lipopolisacáridos (LPS), que son reconocidas por los TLR. Los linfocitos B tienen dos TLR que median la señalización por LPS: TLR4 y PR105 (CD180). La importancia de los TLR en el estado de procoagulación de las células endoteliales en el SAF fue propuesto recientemente por Meroni y cols (124), los cuales demostraron el papel de la vía de señales de traducción del MyD88 en la activación de las células endoteliales por los anticuerpos anti-• 2GPI. Los anticuerpos reaccionaron con la ß2GPI en asociación con la familia del receptor de TLR/IL-1 en la superficie de las células endoteliales (124).

Consideraciones terapéuticas

Como ha sido resumido anteriormente, existe suficiente evidencia científica que indica una etiología infecciosa del SAF. Esto genera la importante pregunta de si se debe iniciar una terapia antibiótica, como tratamiento preventivo o terapéutico, especialmente en el SAFC. Se requiere más información para resolver este enigma. Ello dependerá de si el mecanismo de la enfermedad es puntual (125,126) o es una estimulación continua al sistema inmunológico. El estudio que mostró que el SAF fue controlado mediante la erradicación del *H. pylori* con terapia antibiótica (85) remarca el impacto de la presencia continua de una bacteria en la inducción de la enfermedad. En otro estudio que empleó un modelo experimental de SAF, el tratamiento con ciprofloxacino mejoró el cuadro clínico por inducción de IL-3 y expresión de GM-CSF (127). Estos trabajos apoyarían el uso del tratamiento antibiótico en la terapia de los pacientes con SAF. La utilización de inmunoglobulinas endovenosas (Ig ev) para los casos graves de SAF, como el SAFC, debería ser recomendada, teniendo en cuenta el mecanismo anti-idiotipo de la Ig ev (128-130), como también los amplios efectos antibacterianos y antivirales (131,132).

Referencias

1. Oldstone MB. Molecular mimicry and immune-mediated diseases. FASEB J 1998; 12: 1255-1265
2. Karlsen AE, Dyrberg T. Molecular mimicry between non-self, modified self and self in autoimmunity. Semin Immunol 1998;10:25-34
3. Albert LJ, Inman RD. Molecular mimicry and autoimmunity. N Engl J Med. 1999;341: 2068-2074
4. Regner M, Lambert PH. Autoimmunity through infection or immunization? Nature Immunol 2001;2:185-188
5. Wucherpfennig KW. Structural basis of molecular mimicry. J Autoimmunity 2001;16:293-302
6. Fujinami RS, Oldstone MB. Amino acid homology between the encephalitogenic site of myelin basic protein and virus: mechanism for autoimmunity. Science 1985:230:1043-1045
7. Singh VK, Kalra HK, Yamaki K, et al. Molecular mimicry between a uveitopathogenic site of S-antigen and viral peptides. Induction of experimental autoimmune uveitis in Lewis rats. J Immunol 1990;144: 1282-1287
8. Zhao ZS, Granucci F, YehL, et al. Molecular mimicry by herpes simplex virus-type 1: autoimmune disease after viral infection. Science 1998; 279: 1344-1347
9. Gautam AM, Liblau, R, Chelvanayagam G, et al. A viral peptide with limited homology to a self peptide can induce clinical signs of experimental autoimmune encephalomyelitis. J Immunol 1998;161: 60-64
10. Levin MC, Lee SM, Kalume F, et al. Autoimmunity due to molecular mimicry as a cause of neurological disease. Nat Med 2002; 8:509-513
11. Blank M, Krause I, Fridkin M, et al. Bacterial induction of autoantibodies to beta2-glycoprotein-I accounts for the infectious etiology of antiphospholipid syndrome. J Clin Invest 2002; 109:797-804
12. Shoenfeld Y. Etiology and pathogenetic mechanisms of the antiphospholipid syndrome unraveled. Trends Immunol 2003; 24:2-4
13. Gharavi AE, Pierangeli SS, Colden-Stanfield M, et al. GDKV-induced antiphospholipid antibodies enhance thrombosis and activate endothelial cells in vivo and in vitro. J Immunol 1999; 163:2922-2927
14. Gharavi AE, Pierangeli SS, Espinola RG, et al. Antiphospholipid antibodies induced in mice by immunization with a cytomegalovirus-derived peptide cause thrombosis and activation of endothelial cells in vivo. Arthritis Rheum 2002; 46:545-552
15. Harris EN, Gaharavi AE, Boey ML, et al: Anticardiolipin antibodies: detection by radioimmunoassay and association with thrombosis in systemic lupus erythematosus. Lancet 1983;2:1211-1214
16. Hughes GRV, Harris EN, AE Gharavi. The anti-cardiolipin syndrome. J Rheumatol 1986; 13:486-489
17. Asherson RA, Cervera R, Piette JC, et al. Milestones in the antiphospholipid syndrome. In: Asherson RA, Cervera R, Piette JC, Shoenfeld Y, (eds). The antiphospholipid syndrome II - Autoimmune thrombosis. Elsevier, Amsterdam, 2002
18. Galli M, Comfurious P, Massen C, et al. Anti-cardiolipin antibodies (ACA) directed not to cardiolipin but to a plasma protein cofactor. Lancet 1990; 335:1544-1547
19. Cervera R, Piette JC, Font J, et al: Clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthritis Rheum 2002; 46: 1019-1027
20. Asherson RA and Cervera R. The antiphospholipid syndrome: multiple faces beyondthe classical presentation. Autoimm Rev 2003;2:140-151
21. Shoenfeld Y. Systemic antiphospholipid syndrome. Lupus 2003;497-498
22. Schwarzenbacher R, Zeth K, Diederichs K, et al. Crystal structure of human beta2-glycoprotein I: implications for phospholipid binding and the antiphospholipid syndrome. EMBO J 1999;18:6228-6239
23. Bouma B, de Groot PG, Jean M.H. van den Elsen JML , Ravelli RBG, Schouten A, Simmelink MJA, Derksen RWM, Kroon J, Gros P. Adhesion mechanism of human beta$_2$-glycoprotein I to phospholipids based on its crystal structure EMBO J 1999;18: 5166-5174
24. Brighton TA, Hogg PJ, Dai YP, et al. Beta 2 lycoprotein I in thrombosis: evidence for a role as a natural anticoagulant. Br J Haematol 1996;93: 185-194
25. Koike T, Ichikawa K, Atsumi T, et al. Beta 2-glycoprotein I-anti-beta 2-glycoprotein I interaction. J Autoimmun 2000;15:97-100
26. Manfredi AA, Rovere P, Heltai S, et al. Apoptotic cell clearance in systematic lupus erythematosus II. Role of ?-glycoprotein I. Arthritis Rheum. 1998;41: 215-223
27. Gharavi AE, Sammaritano LR, Wen J, et al. Induction of antiphospholipid antibodies by immunization with ß$_2$-glycoprotein I (apolipoprotein H). J Clin Invest. 1992;90:1105-1111
28. Pierangeli SS, Harris EN. Induction of phospholipid-binding antibodies in mice and rabbits by immunization with human ß$_2$-glycoprotein I or anticardiolipin antibodies alone. Clin Exp Immunol. 1993;93: 269-273
29. Blank M, Faden D, Tincani A, et al. Immunization with anticardiolipin cofactor (ß$_2$-glycoprotein-I) induces experimental APS in naive mice. J Autoimmun 1994;7:441-447
30. Garcia C, Kanbour-Shakir A, Tang H, et al. Induction of experimental antiphospholipid syndrome in PL/J mice following immunization with ß$_2$-glycoprotein I. J Invest Med 1996; 44:69A
31. Aron A L, Cuellar RL, Brey RL, et al. Early onset of autoimmunity in MRL/++ mice following immunization with ß$_2$-glycoprotein I. Clin Exp Immunol. 1995;101:78-82
32. Blank M, George J, Barak V, et al. Oral Tolerance to Low Dose ß$_2$-Glycoprotein I: Immunomodulation of experimental antiphospholipid syndrome. J Immunol 1998;161: 5303-5312
33. Shi W, Chong BH, Chesterman CN. Beta 2-glycoprotein I is a requirement for anticardiolipin antibodies binding to activated platelets: differences with lupus anticoagulants. Blood 1993;81:1255-1262
34. Kornberg A, Blank M, Kaufman S, et al. Induction of tissue factor-like activity in monocytes by anti-cardiolipin antibodies. J Immunol 1994; 153:1328-1332
35. Amengual O, Atsumi T, Khamashta MA, et al. The role of the tissue factor pathway in the hypercoagulable state in patients with the antiphospholipid syndrome. Thromb Haemost 1998;79:276-281
36. Sthoeger ZM, Mozes E, Tartakovsky B. Anti-cardiolipin antibodies induce pregnancy failure by impairing embryonic implantation. Proc Natl Acad Sci USA 1993;90:6464-6467
37. Gharavi AE, Pierangeli SS, Colden-Stanfield M, et al. GDKV-induced antiphospholipid antibodies enhance thrombosis and activate endothelial cells in-vivo and in-vitro. J Immunol 1999;163:2922-2927
38. Blank M, Shoenfeld Y, Cabilli S, et al. Prevention of experimental antiphospholipid syndrome and endothelial cell activation by synthetic peptides. Proc Natl Acd Sci 1999;96:5164-5168
39. Meroni PL, Raschi E, Testoni C, Tincani et al. Statins prevent endothelial cell activation induced by antiphospholipid (anti-beta2-glycoprotein I) antibodies: effect on the proadhesive and proinflammatory phenotype. Arthritis Rheum 2001;44:2870-2878
40. Pierangeli SS, Liu X, Espinola R, et al. Functional analyses of patient-derived IgG monoclonal anticardiolipin antibodies using in vivo thrombosis and in vivo microcirculation models. Thromb Haemost 2000; 84:388-395
41. Branch DW, Dudley DJ, Mitchell MD, et al. Immunoglobulin G fractions from patients with anti-phospholipid antibodies cause fetal death in BALBA/c mice: a model for autoimmune fetal loss. Am J Obstet Gynecol 1990;163:210-216
42. Blank M, Cohen J, Toder V, et al. Induction of primary anti-phospholipid syndrome in mice by passive transfer of anti-cardiolipin antibodies. Proc Natl Acad Sci (USA) 1991; 88:3069-3073
43. Holers VM, Girardi G, Mo L, et al. Complement C3 activation is required for antiphospholipid antibody-induced fetal loss. J Exp Med 2002; 195:211-220
44. Blank M, Waisman A, Mozes E, et al. Characteristics and pathogenic role of anti-beta2-glycoprotein I single-chain Fv domains: induction of experimental antiphospholipid syndrome. Int Immunol 1999;11: 1917-1926
45. Hunt J, Krilis S. The fifth domain of beta 2-glycoprotein I contains a phospholipid binding site (Cys281-Cys288) and a region recognized by anticardiolipin antibodies. J Immunol 1994;152:653-659
46. Iverson GM, Victoria EJ, Marquis DM: Anti-beta2 glycoprotein I (beta 2GPI) autoantibodies recognize an epitope on the first domain of beta2GPI. Proc Natl Acad Sci U S A 1998;95:15542-15546
47. Igarashi M, Matsuura E, Igarashi Y, et al. Human beta2-glycoprotein I as an anticardiolipin cofactor determined using mutants expressed by a baculovirus system. Blood 1996;87:3262-3270
48. Wang MX, Kandiah DA, Ichikawa K, et al. Epitope specificity of monoclonal anti-beta 2-glycoprotein I antibodies derived from patients with the antiphospholipid syndrome. J Immunol 1995; 155:1629-1636
49. Gharavi AE, Pierangeli SS, Colden Stanfield M, et al. GDKV-induced antiphospholipid antibodies enhance thrombosis and activate endothelial cells in vivo and in vitro. J Immunol 1999; 163:2922-2927
50. Arai T, Yoshida K, Kaburaki J, et al. Autoreactive CD4(+) T-cell clones to beta2-glycoprotein I in patients with antiphospholipid syndrome: preferential recognition of the major phospholipid-binding site. Blood 2001; 98:1889-1896
51. Hong DP, Hagihara Y, Kato H, et al. Flexible loop of beta 2-glycoprotein I domain V specifically interacts with hydrophobic ligands. Biochemistry 2001;40:8092-8100
52. Ito H, Matsushita S, Tokano Y, et al. Analysis of T cell responses to the beta 2-glycoprotein I-derived peptide library in patients with anti-beta 2-glycoprotein I antibody-associated autoimmunity. Hum Immunol 2000;61:366-377
53. Visvanathan S, Scott JK, Hwang KK, et al. Identification and characterization of a peptide mimetic that may detect a species of disease

-associated anticardiolipin antibodies in patients with the antiphospholipid syndrome. Arthritis Rheum 2003;48:737-745
54. Shoenfeld Y, Krause I, Kvapil F, et al. Prevalence and clinical correlations of antibodies against six b2-glycoprotein-i-related peptides in the antiphospholipid syndrome. J Clin Immunol. 2003; 23: 377-383
55. Matsuura E, Igarashi Y, Yasuda T, et al. Anticardiolipin antibodies recognize beta 2-glycoprotein I structure altered by interacting with an oxygen modified solid phase surface. J Exp Med 1994;179:457-462
56. Horkko S, Miller E, Branch DW, et al. The epitopes for some antiphospholipid antibodies are adducts of oxidized phospholipid and beta2 glycoprotein 1 (and other proteins). Proc Natl Acad Sci (USA). 1997;94:10356-10361
57. Levine JS, Branch DW, Rauch J. The antiphospholipid syndrome. N Engl J Med 2002; 346:752-763
58. Rauch J, Subang R, D'Agnillo P, et al. Apoptosis and the antiphospholipid syndrome. J Autoimmun. 2000; 15:231-235
59. D'Agnillo P, Levine JS, Subang R, et al. Prothrombin binds to the surface of apoptotic, but not viable, cells and serves as a target of lupus anticoagulant autoantibodies. J Immunol 2003;170:3408-3422
60. Sorice M, Circella A, Misasi R, et al. Cardiolipin on the surface of apoptotic cells as a possible trigger for antiphospholipids antibodies. Clin Exp Immunol 2000; 122:277-2784
61. Cocca BA, Seal SN, D'Agnillo P, et al. Structural basis for autoantibody recognition of phosphatidylserine-beta 2 glycoprotein I and apoptotic cells. Proc Natl Acad Sci U S A 2001; 98:13826-31
62. Dalekos GN, Zachou K, Liaskos C. The Antiphospholipid Syndrome and Infection. Current Rheumatology Reports 2001; 3: 277-285
63. Zandman -Goddard G, Blank M, Shoenfeld Y. Antiphospholipid antibodies and Infections – Drugs. In: The Antiphospholipid Syndrome II. Autoimmune Thrombosis. Asherson RA Cervera R, Shoenfeld Y, Piette J- C. (Eds) (Elsevier) 2002; pp 343-358
64. Uhtman IW, Gharavi AE. Viral Infections and Antiphospholipid Antibodies. Semin Arthritis Rheum 2002;31: 256 – 263
65. Asherson RA, Cervera R. Antiphospholipid Antibodies and Infections. Ann Rheum Dis 2003;62:388-393
66. Cervera R, Asherson RA, Acevedo ML, et al. Antiphospholipid syndrome associated with infections: Clinical and microbiological characteristics of 100 patients. Ann Rheum Dis 2004; 63: 1312-1317
67. Asherson RA. The Catastrophic Antiphospholipid Syndrome. J Rheumatol 1992;19:508 –512
68. Asherson RA, Cervera R, Piette JC, et al. Catastrophic antiphospholipid syndrome. Clinical and laboratory features of 50 patients. Medicine (Baltimore) 1998;77:195-207
69. Asherson RA, Cervera R, Piette JC, et al. Catastrophic antiphospholipid syndrome: Clues to the pathogenesis from a series of 80 patients. Medicine (Baltimore) 2001; 80:355-377
70. Cervera R, Gómez-Puerta JA, Espinosa G, et al. A review of 200 cases from the International Registry of patients with the Catastrophic Antiphospholipid Syndrome (CAPS). Ann Rheum Dis 2003; 62 (suppl.1): 88
71. Asherson RA. The pathogenesis of the catastrophic antiphospholipid syndrome. J Clin Rheumatol 1999; 4:249 –252
72. Rojas – Rodriguez J, Garcia – Carrasco M, Ramos – Casals M, et al.Catastrophic antiphospholipid syndrome: Clinical description and triggering factors in 8 patients. J Rheumatol. 2000;238-240
73. Undas A, Swadzba J, Undas R, et al. Three episodes of acute multiorgan failure in a woman with secondary antiphospholipid syndrome. Pol Arch Med Wewn 1998;56-60
74. Hayem G, Kassis N, Nicaise P, et al. Systemic lupus erythematosus associated with catastrophic antiphospholipid syndrome occurring after typhoid fever. A possible role of Salmonella lipopolysaccharide in the occurrence of diffuse vasculopathy – coagulopathy. Arthritis Rheum 1999;1056-1061
75. Uhtman I, Taher A, Khalil I, et al. Catastrophic antiphospholipid syndrome associated with typhoid fever: Comment on the article by Hayem et al. Arthritis Rheum. 2002;46:850
76. Asherson R, Cervera R, de Groot PG Erkan D, et al. Catastrophic antiphospholipid syndrome: international consensus statement criteria and treatment guidelines. Lupus, 2003; 12:530-534
77. Ehrenfeld M, Bar-Natan M, Sidi Y, et al. Antiphospholipid antibodies associated with severe malaria infection. Lupus.2002;611
78. Levy R. Personal communication.2004
79. Chapman J. Personal communication.2004
80. Amital H, Levy Y, Davidson C, et al.Catastrophic antiphospholipid syndrome: Remission following leg amputation in 2 cases. Semin Arthritis Rheum. 2001;31:127-32
81. Asherson RA, Shoenfeld Y. The role of Infection in the pathogenesis of catastrophic antiphospholipid syndrome –molecular mimicry J Rheumatol 2000;27:12 – 14
82. Gharavi EE, Chaimovich H, Cucurull E, et al. Induction of antiphospholipid antibodies by immunization with synthetic viral and bacterial peptides. Lupus 1999; 8:449-455
83. Gharavi AE, Pierangeli SS, Harris EN. Viral origin of antiphospholipid antibodies: endothelial cell activation and thrombus enhancement by CMV peptide-induced APL antibodies. Immunobiology 2003;207: 37-42
84. Alm RA, Ling LSL, Moir DT, et al. Genomic-sequence comparison of two unrelated isolates of the human gastric pathogen Helicobacter pylori . Nature 1999;397:176-180
85. Cicconi V, Carloni E, Franceschi F, et al. Disappearance of antiphospholipid antibodies syndrome after Helicobacter pylori eradication. Am J Med 2001;111:163-164
86. Eslick GD, Yan P, Xia HH, et al. Foetal intrauterine growth restrictions with Helicobacter pylori infection. Aliment Pharmacol Ther 2002;16: 1677-1682
87. Figura N, Piomboni P, Ponzetto A, et al. Helicobacter pylori infection and infertility. Eur J Gastroenterol Hepatol. 2002;14:663-669
88. Aguejouf O, Mayo K, Monteiro L, et al. Increase of arterial thrombosis parameters in chronic Helicobacter pylori infection in mice. Thromb Res 2002; 108:245-248
89. Grau AJ, Buggle F, Lichy C, et al. Helicobacter pylori infection as an independent risk factor for cerebral ischemia of atherothrombotic origin. J Neurol Sci. 2001;186:1-5
90. Pellicano R, Broutet N, Ponzetto A, et al. Helicobacter pylori: from the stomach to the heart. Eur J Gastroenterol Hepatol. 1999;11:1335-1337
91. Sorice M, Pittoni V, Griggi T, et al. Specificity of anti-phospholipid antibodies in infectious mononucleosis: a role for anti-cofactor protein antibodies. Clin Exp Immunol. 2000;120:301-306
92. Tomb JF, White O, Kerlavage AR, et al. The complete genome sequence of the gastric pathogen Helicobacter pylori. Nature. 1997;388: 539-547
93. Krisher K, Cunningham M W. Myosin : A link between streptococci and heart: Science. 1985;227:413-415
94. M.S.Bronze, J.B. Dale. Epitopes of Streptococcal M proteins that evoke antibodies that cross-react with human brain. J Immunol 1993;151,1: 2820-2828
95. Benoist C, Mathis D: Autoimmunity provoked by infection: how good is the case for T cell epitope mimicry? Nat Immunol 2001;2:797-801
96. Benhamou C, Gauvain JB, Meyer O, et al. Anti-cardiolipin antibodies in Lyme disease. Rev Rhum Mal Osteoartic 1987;54:397-399
97. Garcia Monco JC, Wheeler CM, Benach JL, et al. Reactivity of neuroborreliosis patients (Lyme disease) to cardiolipin and gangliosides. J Neurol Sci 1993;117:206-214
98. Shafran I, Piromalli C, Decker JW, et al. Seroreactivities against Saccharomyces cerevisiae and Mycobacterium avium subsp. paratuberculosis p35 and p36 antigens in Crohn's disease patients. Dig Dis Sci 2002; 47:2079-2081
99. Aichbichler BW, Petritsch W, Reicht GA, et al. Anti-cardiolipin antibodies in patients with inflammatory bowel disease. Dig Dis Sci 1999;44:852-856
100. Thong BY, Chng HH, Ang CL, et al. Recurrent venous thromboses, anti-cardiolipin antibodies and Crohn's disease. QJM 2002;95:253-255
101. Koutroubakis IE, Petinaki E, Anagnostopoulou E, et al. Anti-cardiolipin and anti-beta2-glycoprotein I antibodies in patients with inflammatory bowel disease. Dig Dis Sci 1998; 43:2507-2512
102. Krause I, Monselise Y, Milo G, et al. Anti-Saccharomyces cerevisiae antibodies—a novel serologic marker for Behcet's disease. Clin Exp Rheumatol 2002;20(Suppl 26):S21-24
103. Houman H, Lamloum M, Ben Ghorbel I, et al. Vena cava thrombosis in Behcet's disease. Analysis of a series of 10 cases. Ann Med Interne (Paris). 1999;150:587-590
104. El-Ageb EM, Al-Maini MH, Al-Shukaily AK, et al. Clinical features of Behcet's disease in patients in the Sultanate of Oman; the significance of antiphospholipid antibodies? Rheumatol Int 2002;21:176-181
105. Mukai Y, Tsutsui H, Todaka K, et al. Total occlusion of inferior vena cava in a patient with antiphospholipid antibody syndrome associated with behcet's disease. Jpn Circ J 2001; 65:837-838
106. Famularo G, Antonelli S, Barracchini A, et al. Catastrophic antiphospholipid syndrome in a patient with Behcet's disease. Scand J Rheumatol 2002; 31:100-102
107. Wiles AP, Shaw G, Bright J, et al. NMR Studies of a viral protein that mimics the regulators of complement activation: J Mol Biol 1997;272: 253-265
108. Breman JG, Isao Arita I, Fenne F: Preventing the Return of Smallpox. N Eng J Med 2003; 348:463-466
109. Bouillie S, Barel M, Frade R. Signaling through the EBV/C3d receptor (CR2, CD21) in human B lymphocytes: activation of phosphatidylinositol 3-kinase *via* a CD19-independent pathway. J Immunol 1999; 162:136-143
110. Sorice M, Pittoni V, Griggi T, et al. Specificity of anti-phospholipid

antibodies in infectious mononucleosis: a role for anti-cofactor protein antibodies. Clin Exp Immunol 2000;120:301-306
111. Manfredi AA, Rovere P, Heltai S, et al. Apoptotic cell clearance in systemic lupus erythematosus. II. Role of beta2-glycoprotein I. Arthritis Rheum 1998;41:215-223
112. Rovere P, Sabbadini MG, Vallinoto C, et al. Dendritic cell presentation of antigens from apoptotic cells in a proinflammatory context: role of opsonizing anti-beta2-glycoprotein I antibodies. Arthritis Rheum 1999; 42:1412-1420
113. Kobayashi K, Matsuura E, Liu Q, et al. A specific ligand for beta(2)-glycoprotein I mediates autoantibody-dependent uptake of oxidized low density lipoprotein by macrophages. J Lipid Res 20001;42:697-709
114. Salmon JE, Girardi G, Holers VM. Complement activation as a mediator of antiphospholipid antibody induced pregnancy loss and thrombosis. Ann Rheum Dis 2002;61 Suppl 2:ii46-50
115. Caucheteux SM, Kanellopoulos-Langevin C, Ojcius DM. At the innate frontiers between mother and fetus: linking abortion with complement activation. Immunity 2003;18:169-172
116. Holers VM, Girardi G, Mo L, et al. Complement C3 activation is required for antiphospholipid antibody-induced fetal loss. J Exp Med 2002; 195:211-220
117. Hsu EC, Sabatinos S, Hoedemaeker FJ, et al. Use of site-specific mutagenesis and monoclonal antibodies to map regions of CD46 that interact with measles virus H protein. Virology 1999; 258:314-326
118. Medzhitov R, Janeway Jr C. Innate immunity. N Eng J Med 2000;343: 338-344
119. Akira S, Takeda K, Kaisho T. Toll-like receptors: critical proteins linking innate and acquired immunity, Nat ImmunoL 2001;2:675-680
120. Krieg AM. A role for Toll in autoimmunity. Nat Immunol 2002;3:423-424
121. Leadbetter EA, Rifkin IR, Marshak-Rothstein A. Toll-like receptors and activation of autoreactive B cells. Curr Dir Autoimmun 2003;6:105-122
122. Leadbetter EA, Rifkin IR, Hohlbaum AM, et al. Chromatin-IgG complexes activate B cells by dual engagement of IgM and Toll-like receptors. Nature 2002;416:603-607
123. Hemmi H, Takeuchi O, Kawai T, et al. A Toll-like receptor recognizes bacterial DNA. Nature 2000;408:740-745
124. Raschi E, Testoni C, Bosisio D, et al. Role of the MyD88 transduction signaling pathway in endothelial activation by antiphospholipid antibodies, Blood 2003; 101:3495-3500
125. Gallagher A, Perry J, Freeland J, et al. Hodgkin lymphoma and Epstein-Barr virus (EBV): no evidence to support hit-and-run mechanism in cases classified as non-EBV-associated. Int J Cancer 2003;104:624-630
126. Scarisbrick A, Rodríguez M. Hit-hit and hit-run: viruses in the playing field of multiple sclerosis. Curr Neurol Neurosci Rep 2003;3:265-271
127. Blank M, George J, Fishman P, et al. Ciprofloxacin immunomodulation of experimental antiphospholipid syndrome associated with elevation of interleukin-3 and granulocyte-macrophage colony-stimulating factor expression. Arthritis Rheum 1998;41:224-232
128. Dietrich G, Kaveri SV, Kazatchkine MD. Modulation of autoimmunity by intravenous immune globulin through interaction with the function of the immune/idiotypic network. Clin Immunol Immunopathol 1992;62: S73-81
129. Bakimer R, Blank M, Kosashvilli D, et al. Antiphospholipid syndrome and the idiotypic network. Lupus 1995;4:204-208
130. Bakimer R, Guilburd B, Zurgil N, et al. The effect of intravenous gamma-globulin on the induction of experimental antiphospholipid syndrome. Clin Immunol Immunopathol 1993; 69:97-102
131. Krause I, Wu R, Sherer Y, et al. *In vitro* antiviral and antibacterial activity of commercial intravenous immunoglobulin preparations -a potential role for adjuvant intravenous immunoglobulin therapy in infectious diseases. Transfus Med 2002;12:133-139
132. Shoenfeld Y. Common infections, idiotypic dysregulation, autoantibody spread and induction of autoimmune diseases. J Autoimmun 1996;9: 235-239

EXTENDED REPORT

The acute respiratory distress syndrome in catastrophic antiphospholipid syndrome: analysis of a series of 47 patients

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Background: The acute respiratory distress syndrome (ARDS) is a non-cardiogenic form of pulmonary oedema characterised by severe hypoxaemia refractory to oxygen therapy, with diffuse pulmonary infiltrates on chest radiographs. It can be precipitated by various serious medical and surgical conditions, including systemic autoimmune diseases. The ''catastrophic'' variant of the antiphospholipid syndrome (APS) is an accelerated form of this systemic autoimmune condition which results in multiorgan failure because of multiple small vessel occlusions.

Objective: To analyse the clinical and laboratory characteristics of patients with catastrophic APS who develop ARDS.

Methods: Cases with ARDS were selected from the web site based international registry of patients with catastrophic APS (CAPS registry) (http://www.med.ub.es/MIMMUN/FORUM/CAPS.HTM) and their characteristics examined.

Results: Pulmonary involvement was reported in 150 of 220 patients with catastrophic APS (68%) and 47 patients (21%) were diagnosed as having ARDS. Nineteen (40%) of these patients died. Pathological studies were undertaken in 10 patients and thrombotic microangiopathy was present in seven. There were no differences in age, sex, precipitating factors, clinical manifestations, or mortality between catastrophic APS patients with and without ARDS.

Conclusions: ARDS is the dominant pulmonary manifestation of catastrophic APS. Thus the existence of ARDS in the context of an APS makes it necessary to rule out the presence of the catastrophic variant of this syndrome.

The acute respiratory distress syndrome (ARDS) is a non-cardiogenic form of pulmonary oedema characterised by severe hypoxaemia refractory to oxygen therapy, with diffuse pulmonary infiltrates on chest radiographs.[1] It can be precipitated by various serious medical and surgical conditions.[2] Common causes include pneumonia, aspiration of gastric contents, sepsis, severe trauma with shock, and multiple transfusions.[1 2] In the context of autoimmune diseases, several case reports have suggested that systemic lupus erythematosus (SLE) may be linked to ARDS.[3–7]

In 1992, a new subset of the antiphospholipid syndrome (APS) was described, termed ''catastrophic APS''[8] or Asherson's syndrome,[9] which has an acute and accelerated course. It is characterised by multiple vascular occlusive events, usually affecting small vessels, presenting over a short period of time, with laboratory confirmation of the presence of antiphospholipid antibodies (aPL).[10] Several reviews have been published on a growing number of patients with this condition over the past few years.[11–13] As more and more cases are documented, it has become obvious that there is an inordinately high frequency of pulmonary manifestations in the syndrome (particularly, ARDS), not seen with simple or ''classic'' APS.

Our objective in the present study was to analyse the clinical and laboratory characteristics of patients with catastrophic APS who develop ARDS.

METHODS

We analysed the web site based international registry of patients with catastrophic APS (the CAPS registry; http://www.med.ub.es/MIMMUN/FORUM/CAPS.HTM) which, until February 2004 included 220 patients: 153 female and 67 male; mean (SD) age, 38 (14) years, range 7 to 74; 106 with primary APS, 88 with SLE, 11 with lupus-like syndrome, and 15 with other diseases.

We selected those patients diagnosed by their physicians in charge as having ARDS (ratio of Pao_2 to fraction of inspired oxygen (Fio_2) less than 200; evidence of bilateral infiltrates on chest radiographs; and no reason to suspect that the pulmonary oedema was cardiogenic).[14 15] We included only cases with well documented clinical reports and fulfilling the classification criteria for catastrophic APS. Briefly, these criteria include evidence of involvement in three or more organs, systems, or tissues, development of manifestations simultaneously or in less than a week, confirmation by histopathology of small vessel occlusion in at least one organ or tissue, and laboratory confirmation of the presence of aPL.[10]

We summarised data from these patients using a standardised form, including sex, age, diagnosis of the underlying disorder, main clinical manifestations, immunological features, treatment, and outcome. To facilitate synthesis of the data, we categorised patients into three major diagnoses according to their underlying disease or syndrome:

- SLE if they met four or more of the American College of Rheumatology criteria[16];

Abbreviations: aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; ARDS, acute respiratory distress syndrome; BALF, bronchoalveolar lavage fluid; SIRS, systemic inflammatory response syndrome

- "lupus-like" syndrome if they met two or three American College of Rheumatology criteria;
- primary APS if they met criteria of the International Consensus Statement on preliminary classification for definite APS[17] and did not meet the above criteria for SLE or lupus-like disease.

Fisher's exact test (bilateral) was employed for the statistical analysis, using the SPSS 10.0 statistical program.

RESULTS

General characteristics

Among the 220 patients included in the CAPS registry, pulmonary involvement was described in 150 patients (68%), and data suggesting ARDS were reported in 56 (25%). However, nine patients were excluded: three because of the presence of pneumonia as a cause of the ARDS, three because features of cardiac insufficiency were present, two because diffuse alveolar haemorrhage was revealed by biopsy, and one because necropsy revealed carcinoma of unknown origin. Thus 47 patients in all (21%) were considered to have ARDS, representing nearly one third (31%) of those having pulmonary involvement. The mean (SD) age of the patients with ARDS was 34 (16) years (range 9 to 74). Thirty six (77%) were female, 22 (47%) had SLE, 19 (40%) had primary APS, and 5 (11%) had lupus-like disease (in one case, this information was not available).

Precipitating factors and clinical manifestations

The general characteristics and precipitating factors of the catastrophic APS are summarised in table 1. In 17 patients (36%), precipitating factors were not identified. The most striking precipitating factor, found in 15 patients (32%), was infection, ranging from upper respiratory tract infections to gastrointestinal infections and other septic conditions such as urinary tract infection. Common causes of ARDS such as pneumonia or sepsis appeared to be precipitating factors of catastrophic APS in three patients. The second most frequent precipitating factor, found in six patients (13%), was surgery and invasive procedures, ranging from an endoscopic retrograde cholangio-pancreatography to various major operations. Others were associated with drug treatment (11%), obstetric complications (9%), SLE flares (4%), or withdrawal of anticoagulants (2%).

Intra-abdominal involvement was identified in 42 patients (89%), mainly consisting of renal (81%), hepatic (26%), gastrointestinal (19%), pancreatic (10%), adrenal (17%), and splenic (5%) manifestations. Thirty six patients (77%) had evidence of cerebrovascular complications, mainly encephalopathy and cerebrovascular accidents, but occasionally seizures or transverse myelitis. Skin manifestations were also frequent (55%) and consisted of livedo reticularis, ulcers, digital gangrene, purpura, and microthrombosis of small vessels. Twenty four patients (51%) had cardiac involvement, mainly cardiac failure and confirmed myocardial infarction, Libman-Sacks non-bacterial endocarditis, or silent valve lesions. Peripheral venous thrombosis was present in 12 patients (26%) and peripheral arterial occlusive disease in five (11%).

Other abnormalities occasionally encountered were retinal, pleural, and peripheral nerve lesions.

There were no differences in age, sex, precipitating factors, or clinical manifestations between catastrophic APS patients with and without ARDS.

Laboratory features

The IgG isotype of anticardiolipin antibodies (aCL) was reported as positive in 38 patients (81%) and the IgM aCL in 16 (34%). Lupus anticoagulant was present in 34 patients (72%).

Pathological features

Histopathological study of lungs was undertaken in 10 patients (necropsy in eight, lung biopsy in two). The main finding was non-inflammatory thrombotic microangiopathy which was present in seven patients; intra-alveolar haemorrhage and hyaline membrane formation were each present in two cases. In all cases, pathological examination ruled out vasculitis.

Treatment and outcome

The treatment and outcome of the 47 patients with ARDS and catastrophic APS are shown in table 2. Data on treatment were not available for three patients. Finally, 44 episodes of ARDS were analysed. Anticoagulation was the most frequent treatment, used in 42 patients (95%), followed by steroids in 39 (89%). Immunosuppressants were used in 19 patients (43%) (cyclophosphamide in 18 and vincristine in one), intravenous immunoglobulins were used in 21 patients (48%), and plasma exchange in 15 (34%). Intravenous prostaglandin was used in one case. Nineteen patients died (40%). There was no statistically significant difference in mortality between catastrophic APS with ARDS and without ARDS. No differences were found in the recovery rate depending on the use or not of a particular treatment.

DISCUSSION

ARDS is associated with a variety of clinical disorders. These can be divided into two categories: those associated with direct injury to the lung, with direct effects on pulmonary cells (pneumonia, aspiration of gastric contents, pulmonary contusion, near drowning, and inhalational injury); and those that cause indirect lung injury in the setting of a systemic process through acute systemic inflammatory responses (sepsis, severe trauma with shock and multiple transfusions, cardiopulmonary bypass, drug overdose, and acute pancreatitis).[18] Overall, sepsis is associated with the greatest risk of progression to ARDS (approximately 40%).[19] ARDS has also been documented in patients with SLE,[3–7] which may be complicated by pulmonary hypertension,[4] as well as in adult Still's disease.[20 21] Its occurrence in catastrophic APS is a completely new association. In the present study, we found a frequency of 21% of ARDS in the patients with catastrophic APS.

Although alveolar haemorrhage may be responsible for dyspnoea in patients with catastrophic APS, it is infrequently encountered, probably because it is difficult to diagnose.[22] Once other causes (such as cardiac failure, pneumonia, and recurrent pulmonary emboli) have been excluded clinically and by the appropriate investigations, ARDS is by far the commonest underlying pulmonary condition encountered.

An intriguing question is whether aPL may play a role in the development of ARDS in patients with catastrophic APS or, conversely, whether ARDS is produced by the same factor that precipitates the catastrophic APS—that is, infection or surgery. Although it is difficult to draw any firm conclusion because of the sparse data, several findings point towards a direct link between aPL and ARDS.

The first of these is that the acute phase of ARDS is characterised by an influx of protein-rich oedema fluid, with associated red cells and neutrophils, into the air spaces secondary to increased permeability of the alveolar–capillary barrier.[23] This increase in endothelial and epithelial permeability allows higher molecular weight proteins, such as IgG and IgM, to enter the air spaces.[24] Maneta-Peyret *et al*[25] have reported an increased amount of IgG in the bronchoalveolar lavage fluid (BALF) of patients with ARDS in comparison

Table 1 General characteristics of patients with acute respiratory distress syndrome plus catastrophic antiphospholipid syndrome

Case*	Sex	Age (y)	Diagnosis	Previous APS manifestations	Precipitating factor	Other organ involvement at the time of catastrophic APS	LA	IgG aCL	IgM aCL
1 (2)	M	22	Lupus-like			PVT, CNS, kidney, skin	+	+	+
2 (3)	F	22	Lupus-like			Heart, CNS, kidney, skin, retina	+	+	+
3 (14)	F	11	SLE	Epilepsy	Intestinal infection	CNS, skin, liver	+	−	−
4 (16)	F	23	SLE		ERCP	Heart, CNS, kidney, liver	+	Moderate +	−
5 (20)	F	43	PAPS	DVT, fetal losses		Heart, kidney, GI tract, adrenals	+	276 GPL	−
6 (26)	M	45	SLE	DVT, PE, SVC thrombosis		CNS, central retinal vein thrombi	−	20	−
7 (33)	F	52	Lupus-like	Fetal loss	Diuretic	CNS, kidney, liver, GI tract, pancreas	NR	High +	High +
8 (36)	F	36	PAPS	DVT		Heart, kidney, GI tract, adrenal glands, thyroid, muscle, peripheral nerves	+	95 GPL	−
9 (41)	F	35	PAPS	Fetal loss, PAT, skin ulcers		CNS, kidney	+	46 GPL	4 MPL
10 (43)	M	47	PAPS			CNS	+	−	−
11 (46)	M	55	Lupus-like	DVT	ACE inhibitor	PVT, heart, kidney, skin	+	High +	−
12 (49)	F	74	PAPS	DVT, PE, LR, skin ulcers		Heart, CNS, kidney, retina	+	200 GPL	NR
13 (62)	F	48	PAPS	DVT	Cholectomy, sepsis	Liver, GI tract, peripheral nerves	NR	Moderate +	Moderate +
14 (63)	M	47	PAPS	TIA, CVA, myocardial infarction	Leg ulcer infection	PAT, CNS, kidney, skin	+	+	NR
15 (69)	F	28	SLE		Pneumonia	Heart, kidney, skin, GI tract	NR	+	NR
16 (72)	F	42	SLE	Fetal loss, CVA, LR, thrombocytopenia		Heart, CNS, kidney, skin, liver, spleen	+	72 GPL	NR
17 (74)	F	16	PAPS		Upper respiratory infection	PVT, CNS, skin, peripheral nerves	+	100 GPL	−
18 (76)	F	21	SLE		Upper respiratory infection	PVT, heart, CNS, kidney, skin, transverse myelitis	−	88 GPL	−
19 (77)	F	54	SLE		Cutaneous and urinary infection, abdominal surgery	PVT, heart, skin, liver, transverse myelitis	−	−	96 MPL
20 (78)	F	17	PAPS		OC, sun exposure	PVT, heart, CNS, kidney, skin, transverse myelitis	−	104 GPL	−
21 (82)	F	26	SLE	DVT	Post-fetal loss	CNS, kidney, skin	NR	24 GPL	NR
22 (94)	M	18	SLE			Heart, CNS, kidney, skin, pleura	NR	+	NR
23 (99)	F	33	PAPS	Fetal loss, superficial venous thrombosis	Pregnancy, caesarean section	Heart, CNS, kidney, skin	+	>100 GPL	−
24 (104)	F	28	SLE	DVT, thrombocytopenia		PVT, heart, CNS, kidney	+	+	−
25 (106)	F	67	PAPS		Urinary infection	Heart, CNS, kidney	+	High +	−
26 (108)	F	20	PAPS		Throat infection	PVT, CNS, kidney, skin	−	+	−
27 (110)	F	22	SLE	Fetal loss	HELLP	CNS, kidney, cranial nerve	+	+	+
28 (121)	F	27	PAPS	DVT, fetal loss	Post-fetal loss	Heart, liver	−	72 GPL	−
29 (125)	F	39	Lupus-like	Fetal death, amaurosis fugax, TIA		Heart, CNS, kidney, skin	+	High +	−
30 (127)	F	49	SLE		Major abdominal surgery	PAT, heart, CNS, kidney, skin, GI tract, pancreas	+	128 GPL	−
31 (132)	M	39				Heart, CNS, kidney, skin, adrenal glands	+	174 GPL	−
32 (134)	F	21	PAPS	DVT	Vascular surgery	CNS, kidney, liver	+	High	High +
33 (149)	F	18	SLE	Thrombocytopenia	Respiratory infection	CNS, kidney, spleen, pancreas, thyroid	+	164 GPL	−
34 (158)	M	55	PAPS	DVT	ACE inhibitor	PVT, heart, kidney, skin	+	−	High +
35 (176)	F	47	SLE	LR, thrombocytopenia	Anticoagulation withdrawal	PAT, CNS, skin, adrenal glands	+	NR	NR
36 (177)	F	38	SLE	CVA, Budd-Chiari syndrome, thrombocytopenia	Sepsis	PAT, CNS, skin, adrenal glands	+	Moderate +	High +
37 (178)	F	63	SLE	Fetal loss, LR, Renal microangiopathy, thrombocytopenia,	Major abdominal surgery	PAT, CNS, skin, GI tract, adrenal glands	+	Moderate +	High +
38 (183)	M	15	PAPS			PVT, liver	+	44 GPL	12 MPL
39 (184)	M	33	PAPS	Livedo reticularis, skin ulcers		Heart, CNS, kidney, skin	+	860 GPL	NR
40 (185)	F	52	PAPS	Fetal loss, CVA		CNS	−	Moderate +	−
41 (199)	M	11	SLE			PVT, heart, kidney	+	36 GPL	−
42 (200)	F	9	SLE	LR, digital ulceration	Lupus flare, urinary infection	CNS, skin	−	100 GPL	−
43 (201)	F	31	SLE		Oestrogens	Heart, CNS, kidney, liver, pancreas, myometrium	+	+	+
44 (204)	F	38	SLE		GI infection	CNS, kidney, skin	+	+	+

Table 1 Continued

Case*	Sex	Age (y)	Diagnosis	Previous APS manifestations	Precipitating factor	Other organ involvement at the time of catastrophic APS	LA	IgG aCL	IgM aCL
45 (207)	F	20	PAPS		GI infection	Kidney, GI tract	+	72 GPL	–
46 (211)	F	27	SLE	LR, skin ulcers	Lupus flare	PVT, CNS, kidney, skin, adrenal glands	+	High +	–
47 (213)	F	27	SLE		Upper respiratory infection	Heart, CNS, kidney, liver	+	Moderate +	–

*The numbers in parentheses correspond to the order of the cases in the CAPS registry.
ACE, angiotensin converting enzyme; aCL, anticardiolipin antibodies; APS, antiphospholipid syndrome; CNS, central nervous system; CVA, cerebrovascular accident; DVT, deep venous thrombosis; ERCP, endoscopic retrograde cholangio-pancreatography; F, female; GI, gastrointestinal; HELLP, Haemolysis, Elevated Liver Enzymes, and Low Platelets syndrome; LA, lupus anticoagulant; LR, livedo reticularis; M, male; NR, not recorded; OC, oral contraceptives; PAPS, primary APS; SLE, systemic lupus erythematosus; SVC, superior vena cava; PAT, peripheral artery thrombosis; PE, pulmonary embolism; PVT, peripheral venous thrombosis; TIA, transient ischaemic attack; y, years.

with mechanically ventilated control patients. These antibodies were directed mainly against anionic phospholipids. However, it is difficult to determine whether the presence of these autoantibodies was associated with modifications of the lipid composition of the surfactant or whether they were produced in response to damage to the alveolar or other cell membranes. Furthermore, these antibodies may be produced locally or be provided from plasma following the increased capillary–alveolar permeability present in ARDS. The same group showed that the aPL detected in the BALF of a patient developing ARDS during catastrophic APS did not have the same specificity towards the different phospholipids as aPL in the serum.[26] This supports the hypothesis of local production of aPL. Additionally, a quantitative as well as a qualitative deficiency of surfactant phospholipids was also observed.[26] The investigators suggested that antibodies directed against surfactant phospholipids could cause surfactant abnormalities and a resulting inflammatory reaction. Unfortunately, so far there are no experimental data on a possible effect of aPL on the function of the surfactant.

Table 2 Treatment and outcome of patients with acute respiratory distress syndrome plus catastrophic antiphospholipid syndrome

Case*	Treatment	Outcome
1 (2)	AC, S, CP, PE	Recovery
2 (3)	AC, S, CP, PE	Recovery
3 (14)	AC, S	Recovery
4 (16)		Death
5 (20)		Death
6 (26)	AC, S, CP, PE, GG, vincristine, splenectomy	Death
7 (33)	AC, S, GG	Recovery
8 (36)	S, HD	Death
9 (41)	AC, S, PE, HD	Recovery
10 (43)	AC	Recovery
11 (46)	AC, fibrinolytics	Recovery
12 (49)	AC, S, GG	Recovery
13 (62)	AC, S	Recovery
14 (63)	AC, S, GG	Recovery
15 (69)		Death
16 (72)	AC, S, CP, PE	Death
17 (74)	AC, S	Recovery
18 (76)	AC, S, CP	Death
19 (77)	AC, S, CP	Recovery
20 (78)	AC, S, CP	Death
21 (82)	AC, S, CP	Recovery
22 (94)	S, CP, PE	Death
23 (99)	AC, S, GG	Death
24 (104)	AC, S, GG	Death
25 (106)	AC, S	Death
26 (108)	AC, S, CP, GG	Recovery
27 (110)	AC, S, GG	Recovery
28 (121)	AC, S	Recovery
29 (125)	AC, S, CP, GG, prostacyclin	Recovery.
30 (127)	AC, S, CP, PE, HD	Death
31 (132)	AC, S, PE, GG	Recovery
32 (134)	AC, S, PE, GG, HD	Recovery
33 (149)	AC, S, CP, GG, HD	Death
34 (158)	AC, aspirin	Recovery
35 (176)	AC, S, CP, GG	Death
36 (177)	AC, S, CP, GG	Death
37 (178)	AC, S, GG	Death
38 (183)	AC, S, GG	Recovery
39 (184)	AC	Recovery
40 (185)	AC, S	Recovery
41 (199)	AC, S, CP, PE, GG	Recovery
42 (200)	AC, S, CP, PE, GG	Recovery
43 (201)	AC, S, PE	Recovery
44 (204)	AC, S, PE, HD	Death
45 (207)	AC, S, GG	Recovery
46 (211)	AC, CP, PE, GG	Recovery
47 (213)	AC, S, PE, GG, HD	Death

*The numbers in parentheses correspond to the order of the cases in the CAPS registry.
AC, anticoagulation; CP, cyclophosphamide; GG, intravenous gamma globulin; HD, haemodialysis; PE, plasma exchange; S, steroids S, steroids.

The systemic inflammatory response syndrome (SIRS) secondary to cytokine activation could be another pathogenic mechanism of indirect injury in the ARDS associated to catastrophic APS. A complex network of cytokines initiate and amplify the inflammatory response in ARDS. The extensive tissue damage caused by catastrophic APS results in the liberation of excessive amounts of cytokines. Some of the major clinical manifestations of catastrophic APS resulting from multiple small vessel occlusive disease and consequent tissue necrosis (that is, ARDS and decreased cardiac function) may be directly attributable to SIRS.[27] In support of this is the recent report of a study in which the cytokine levels of a patient with catastrophic APS were evaluated. The study showed that vascular endothelial cell injury might play a major role in the pathogenesis of catastrophic APS.[28] The cytokines involved in ARDS include tumour necrosis factor α, interleukin 1 (IL1), IL6,[29] and macrophage migration inhibitory factor.[30] These have been found to be increased in both sera and BALF of ARDS patients, and they are responsible not only for ARDS but also for the cerebral oedema which may be a factor in the initial confusion and deterioration of consciousness seen in patients with SIRS, as well as the myocardial dysfunction encountered.[30] There appears to be a massive influx of neutrophils into the damaged tissues. The concentration of potent neutrophil chemoattractants, such as IL8, is also increased in BALF.[31] Additionally, IL18—a proinflammatory cytokine which induces the production of several other cytokines—including interferon γ—and enhances T cell and natural killer cell toxicity as well as neutrophil migration and degranulation. It may also be implicated in acute lung inflammation by increasing neutrophil migration and lung vascular permeability. This cytokine may also be implicated in the pathogenesis of ARDS.[29]

Finally, pathological examination of lung specimens from patients with ARDS in catastrophic APS showed extensive

small vessel thromboses, intra-alveolar haemorrhage, and hyaline membrane formation.[32] Interestingly, in our study, the main pathological finding was non-inflammatory thrombotic microangiopathy, present in 70% of the patients with lung specimens. This may produce an increase in vascular permeability, surfactant deficiency, and intra-alveolar inflammation. It is another probable pathogenic mechanism of ARDS and is closely linked to activation of inflammation and coagulation, which is characterised by fibrin deposition in the pulmonary parenchyma, vasculature, and air spaces. This procoagulant state is tissue factor dependent and is associated with increased elaboration of inflammatory cytokines.[33]

Conclusion

ARDS is the dominant pulmonary manifestation of catastrophic APS. Our study shows that catastrophic APS is a major risk factor for the development of ARDS. The presence of ARDS in the context of an APS makes it necessary to rule out the catastrophic variant of this syndrome.

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*The members of the Catastrophic Antiphospholipid Syndrome Registry Project Group are listed in the appendix.

APPENDIX

THE CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME REGISTRY PROJECT GROUP

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REFERENCES

1 **Ware LB**, Matthay MA. The acute respiratory distress syndrome. *N Engl J Med* 2000;**342**:1334–9.
2 **Wyncoll DLA**, Evans TW. Acute respiratory distress syndrome. *Lancet* 1999;**354**:497–501.
3 **Andonopoulos AP**. Adult respiratory distress syndrome: an unrecognized premortem event in systemic lupus erythematosus. *Br J Rheumatol* 1992;**31**:346–8.
4 **Asherson RA**, Ridley M, Fletcher CD, Hughes GRV. Systemic lupus erythematosus, pulmonary hypertension and adult respiratory distress syndrome (ARDS). *Clin Exp Rheumatol* 1988;**6**:301–4.
5 **Domingo-Pedrol P**, Rodriguez de la Serna A, Mancebo-Cortes J, Sanchez-Segura JM. Adult respiratory distress syndrome caused by acute systemic lupus erythematosus. *Eur J Resp Dis* 1985;**67**:141–4.
6 **Kim WU**, Kim SI, Yoo WH, Park JH, Min JK, Kim SC, *et al*. Adult respiratory distress syndrome in systemic lupus erythematosus: causes and prognostic factors: a single center, retrospective study. *Lupus* 1999;**8**:552–7.
7 **Marino CT**, Pertschuck LP. Pulmonary hemorrhage in systemic lupus erythematosus. *Arch Intern Med* 1981;**141**:201–3.
8 **Asherson RA**. The catastrophic antiphospholipid syndrome. *J Rheumatol* 1992;**19**:508–12.
9 **Piette JC**, Cervera R, Levy R, Nasonov EL, Triplett DA, Shoenfeld Y. The catastrophic antiphospholipid syndrome – Asherson's syndrome. *Ann Med Intern* 2003;**154**:95–6.
10 **Asherson RA**, Cervera R, de Groot PR, Erkan D, Boffa M-C, Piette J-C, *et al*. Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines. *Lupus* 2003;**12**:530–4.
11 **Asherson RA**, Cervera R, Piette JC, Font J, Lie JT, Borcoglu A, *et al*. Catastrophic antibody syndrome. Clinical and laboratory features of 50 patients. *Medicine (Baltimore)* 1998;**77**:195–207.
12 **Asherson RA**, Cervera R, Piette JC, Shoenfeld Y, Espinosa G, Petri MA, *et al*. Catastrophic antiphospholipid syndrome: clues to the pathogenesis from a series of 80 patients. *Medicine (Baltimore)* 2001;**80**:355–76.
13 **Cervera R**, Gomez-Puerta JA, Espinosa G, Font J, De la Red G, Gil V, *et al*. CAPS Registry: a review of 200 cases from the International Registry of patients with catastrophic antiphospholipid syndrome (CAPS) [abstract]. *Ann Rheum Dis* 2003;**62**(suppl 1):88.
14 **Bernard GR**, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, *et al*. The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994;**149**:818–24.
15 **Murray JF**, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. *Am Rev Respir Dis* 1988;**138**:720–3.
16 **Hochberg MC**. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. *Arthritis Rheum* 1997;**40**:1725.
17 **Wilson WA**, Gharavi AE, Koike T, Lockshin MD, Branch DW, Piette J-C, *et al*. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. *Arthritis Rheum* 1999;**42**:1309–11.
18 **Gattionini L**, Pelosi P, Suter PM, Pedoto A, Vercesi P, Lissoni A. Acute respiratory distress syndrome caused by pulmonary and extrapulmonary disease: different syndromes? *Am J Resp Crit Care Med* 1998;**158**:3–11.
19 **Hudson LD**, Milberg JA, Anardi D, Maunder RJ. Clinical risks for development of the acute respiratory distress syndrome. *Am J Respir Care Med* 1995;**151**:293–301.
20 **Carron PL**, Surcin S, Plane P, Balvay P, Caps T, Belle F, *et al*. Adult-onset Still's disease: a rare cause of acute respiratory distress. *Rev Med Interne* 2000;**21**:1133–4.
21 **Hirohata S**, Kamoshita H, Taketani T, Maeda S. Adult Still's disease complicated with adult respiratory distress syndrome. *Arch Intern Med* 1986;**146**:2409–10.
22 **Wiedermann FJ**, Mayr A, Schobersberger W, Knotzer H, Sepp N, Rieger M, *et al*. Acute respiratory failure associated with catastrophic antiphospholipid syndrome. *J Intern Med* 2000;**247**:723–30.
23 **Pugin J**, Verghese G, Vidmer M-C, Matthay MA. The alveolar space is the site of intense inflammatory and profibrotic reactions in the early phase of acute respiratory distress syndrome. *Crit Care Med* 1999;**27**:304–12.
24 **Holter JF**, Weiland JE, Pacht ER, Gadek JE, Davis WB. Protein permeability in the adult respiratory distress syndrome: loss of size selectivity of the alveolar epithelium. *J Clin Invest* 1986;**78**:1513–22.
25 **Maneta-Peyret L**, Kitsiouli E, Lekka M, Nakos G, Cassagne C. Autoantibodies to lipids in bronchoalveolar fluid of patients with acute respiratory distress syndrome. *Crit Care* 2001;**29**:1950–4.
26 **Nakos G**, Kitsiouli E, Maneta-Peyret L, Cassagne C, Tsianos E, Lekka M. The characteristics of bronchoalveolar lavage from a patient with antiphospholipid syndrome who develop acute respiratory distress syndrome. *Clin Rheumatol* 2001;**20**:91–7.
27 **Belmont HM**, Abramson SB, Lie JT. Pathology and pathogenesis of vascular injury in systemic lupus erythematosus: interactions of inflammatory cells and activated endothelium. *Arthritis Rheum* 1996;**39**:9–22.
28 **Burcoglu-O'ral A**, Erkan D, Asherson RA. Treatment of catastrophic antiphospholipid syndrome (CAPS) with defibrotide, a proposed vascular endothelial cell modulator. *J Rheumatol* 2002;**29**:2006–11.
29 **Suter PM**, Suter S, Giradin E, Roux-Lombard P, Grau GE, Dayer JM. High bronchoalveolar levels of tumour necrosis factor and its inhibitors, interleukin-1, interferon and elastase, in patients with adult respiratory distress syndrome after trauma, shock or sepsis. *Am Rev Resp Dis* 1992;**145**:1016–22.
30 **Donnelly SC**, Haslett C, Reid PJ, Grant TS, Wallace WA, Metz CN, *et al*. Regulatory role of macrophage migration inhibitory factor in acute respiratory distress syndrome. *Nat Med* 1997;**3**:320–3.
31 **Chollet-Martin S**, Montravers P, Gibert C, Elbim C, Desmonts JM, Fagon JY, *et al*. High levels of interleukin-8 in the blood and alveolar spaces of patients with pneumonia and adult respiratory distress syndrome. *Infect Immun* 1993;**61**:4553–9.
32 **Espinosa G**, Cervera R, Font J, Asherson RA. The lung in the antiphospholipid syndrome. *Ann Rheum Dis* 2002;**61**:195–8.
33 **Welty-Wolf KE**, Caraway MS, Ortel TL, Piantadosi CA. Coagulation and inflammation in acute lung injury. *Thromb Haemost* 2002;**88**:17–25.

4. GROSS WL, HAUSCHILD S, MISTRY N: The clinical relevance of ANCA in vasculitis. *Clin Exp Immunol* 1993; 91 (Suppl. 1): 7-11.
5. GSERNOK E, HOLLE J, HEILMICH B *et al*.: Evaluation of capture ELISA for detection of antineutrophil cytoplasmic antibodies directed against proteinase 3 in Wegner's granulomatosis: first results from multicentre study. *Rheumatology* 2004; 43: 174-80.
6. PASTEUR M, LAROCHE C, KEOGAN M: Pleuropericardial effusion in a 50-year-old woman. *PMJ* 2001; 77: 347, 355-7.
7. POUCHOT J *et al*.: Adult Still's disease: manifestations, disease course, and outcome in 62 patients. *Medicine* 1991; 70: 118-36.
8. WENDING D, HUMBERT PG, BILLEREY C, FAST T, DUPOND JL: Adult onset still's disease and related renal amyloidosis. *Ann Rheum Dis* 1991; 50: 257-9.

Catastrophic antiphospholipid syndrome presenting with renal thrombotic microangiopathy and diffuse proliferative glomerulonephritis

Sirs,

The catastrophic variant of the antiphospholipid syndrome (APS) is an unusual but often lethal form of presentation of this syndrome characterized by a rapid development of multiorganic failure, mainly due to thrombotic microangiopathy in several organs (1). Since the early description of the catastrophic APS (1), more than 300 cases have been collected, being the kidney one of the more commonly affected organs (70%) (2). However, there are no previous reports of the simultaneous presence of diffuse proliferative lupus glomerulonephritis and renal thrombotic microangiopathy (TMA) as the first manifestation of catastrophic APS.

A 29-year-old Caucasian man was admitted at the Emergency Department in June 2004 due to the appearance of generalized oedema in the last 4 weeks accompanied by decrease in urine output. He had been diagnosed as having systemic lupus erythematosus (SLE) in 2002 due to a history of Evans' syndrome, recurrent leg ulcers, presence of antinuclear antibodies (ANA) (1/160), anti dsDNA antibodies (42 U/mL [normal < 7 U/mL]), and lupus anticoagulant (LA), and was on treatment with aspirin alone at the time of admission. Physical examination revealed marked *livedo reticularis* in the lower extremities and a generalized oedema. During the first hours of admission, he presented seizures with a cerebral computed tomography (CT) scan that showed a cortico-subcortical ischaemic lesion and a lacunar infarct in the right semioval region. Transthoracic echocardiography disclosed severe decrease in left ventricular ejection fraction (LVEF) (35%), mild aortic and mitral regurgitation, and a moderate pericardial effusion. Laboratory tests at admission showed microangiopathic haemolytic anaemia (Hb 8.5 g/dL) with schistocytes, elevated serum creatinine (5.6 mg/dL), and prolonged activated partial thromboplastin time. LA was positive, whilst IgG and IgM anticardiolipin antibodies (aCL) were negative. Anti ds-DNA antibodies were positive (> 200 U/mL) and C3, C4 and CH50 complement levels were low. He was admitted at the Intensive Care Unit (ICU) where i.v. methylprednisolone (1 g per day for 5 days) and i.v. cyclophosphamide (1,250 mg) were started. One week later, percutaneous renal biopsy was performed disclosing the presence of diffuse proliferative lupus glomerulonephritis and TMA (Figure 1). A diagnosis of definite catastrophic APS was made (3) and anticoagulation and plasma exchange (PE) sessions were started. One month later, he was discharged of the ICU because of progressive improvement of his clinical condition, including the heart involvement (LVEF > 60%). However, 4 months later, he was admitted again because of fulminant hepatic failure. The patient's clinical condition progressively deteriorated in the following days and died due to multiorgan failure. Autopsy showed multiple liver infarcts, inferior vena cava thrombosis (6.0 x 0.4 cm) and signs of bilateral pneumonia, as well as persistence of the renal TMA previously described.

In the present case, a "double" renal injury was produced probably due to an immune-complex glomerular deposition (SLE nephritis) and an ischaemic glomerular damage (TMA induced by APS) and this was the first clinical manifestation of a catastrophic APS in a patient with SLE, a combination that has not been previously described. Although there are few reports describing the simultaneous presence of proliferative glomerulonephritis and renal TMA in SLE patients (4-7), none of them fulfil the recently proposed criteria for the classification of definite catastrophic APS (3).

This variant of the APS is a life-threatening condition with an elevated mortality rate (around 50%) that requires high clinical awareness. Therefore, it is essential that it should be diagnosed early and treated aggressively. The combination of high doses of heparin plus steroids plus PE and/or intravenous gammaglobulins is the treatment of choice in patients with catastrophic APS (2).

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References

1. ASHERSON RA: The catastrophic antiphospholipid syndrome. *J Rheumatol* 1992; 19: 508-12.
2. ERKAN D, CERVERA R, ASHERSON RA: Catastrophic antiphospholipid syndrome: where do we stand? *Arthritis Rheum* 2003; 48: 3320-7.
3. ASHERSON RA, CERVERA R, DE GROOT PG *et al*.: Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines. *Lupus* 2003; 12: 530-4.
4. MAGIL AB, MCFADDEN D, RAE A: Lupus glomerulonephritis with thrombotic microangiopathy. *Hum Pathol* 1986; 17: 192-4.
5. MUSIO F, BOHEN EM, YUAN CM, WELCH PG: Review of thrombotic thrombocitopenic purpura in the setting of systemic lupus erythematosus. *Semin Arthritis Rheum* 1998: 28: 1-19.
6. CHARNEY DA, NASSAR G, TROUNG L, NADASDY T: "Pauci-Immune" proliferative and necrotizing glomerulonephritis with thrombotic microangiopathy in patients with systemic lupus erythematosus and lupus-like syndrome. *Am J Kidney Dis* 2000; 35: 1193-206.
7. SANTIAGO K, BATUMAN V, MELEG-SMITH S: A 31-year-old woman with lupus erythematosus and fatal multisystemic complications. *J La State Med Soc* 1996; 148: 379-84.

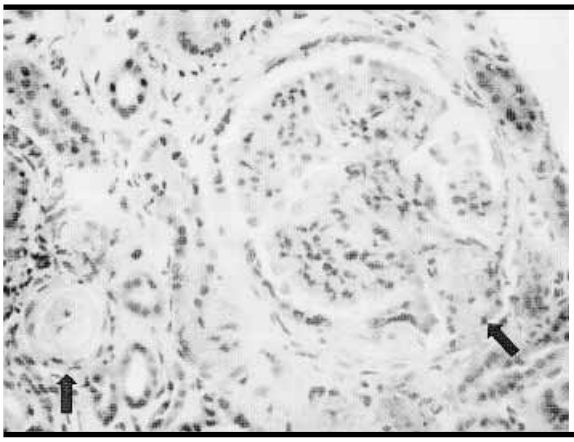

Fig. 1. Percutaneous renal biopsy specimen showing prominent diffuse endocapillar hypercelularity (type IV [WHO classification] lupus glomerulonephritis). Luminar thrombi can be seen in arterioles (**arrows**), small arteries, arterioles and glomerular capillaries. (Hematoxylin & eosin, original magnification x 400).

CONCISE REPORT

Prevalence of the antiphospholipid syndrome in primary systemic vasculitis

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Background: The antiphospholipid (APS or Hughes') syndrome, anticardiolipin antibodies (aCL), and the lupus anticoagulant (LA) are associated with systemic lupus erythematosus, malignancy, infection, and drugs. It has been described in patients with primary systemic vasculitis (PSV).

Objective: To determine the prevalence of APS in patients with PSV attending a vasculitis clinic and the prevalence of patients with positive aCL and/or the LA who do not fulfil the classification criteria for APS.

Methods: All case notes of patients attending the vasculitis clinic over a 12 month period were reviewed. Outpatients and inpatients were both included and were assessed for features of the APS and presence of aPL. Patients with positive aCL or LA tests were classified according to the significance of these results.

Results: Of 144 patients with PSV, 25 had positive aCL or LA on at least one occasion, representing a point prevalence of 17%. Of these, nine had definite APS (classified by the Sapporo criteria) and a further four patients had clinical and serological features of APS, although insufficient to satisfy the Sapporo criteria. Twelve had only positive aPL.

Conclusion: The antiphospholipid syndrome, aCL, and the LA may occur in association with PSV.

The antiphospholipid syndrome (APS or Hughes' syndrome) is associated with systemic lupus erythematosus and other connective tissue diseases, malignancy, infection, and drug induced syndromes. Antiphospholipid antibodies (aPL) and thrombosis may also occur in patients with primary systemic vasculitis (PSV). Several case reports have described APS in individual patients with polyarteritis nodosa,[1–4] microscopic polyangiitis,[5] and, in particular, Wegener's granulomatosis.[6] Other reports describe several patients with giant cell arteritis/polymyalgia rheumatica and APS[7–9] or Behçet's disease and APS.[10] More recently, a high prevalence of aPL has been reported in different vasculitides, including Takayasu's arteritis.[11] However, one prospective study failed to find an increased prevalence of aPL in the systemic vasculitides in comparison with healthy blood donors, though the number of patients studied was small.[12] A further large study of 1000 consecutive patients with APS found only a very small proportion (0.7%) had a diagnosis of systemic vasculitis.[13]

Our experience of patients with PSV suggested that a significant number of these patients have a prothrombotic tendency. We therefore set out to assess the prevalence and clinical associations of aPL in a cohort of current inpatient and clinic attendees over a 12 month period.

METHODS

All attendees at the vasculitis clinic at St Thomas' Hospital over the 12 month period October 2001–October 2002 were reviewed. We also included all inpatients admitted under our care during this time. The case notes were reviewed and only those patients with a definite diagnosis of PSV were included. Patients in whom a diagnosis of systemic lupus erythematosus was suspected were excluded. The 144 patients were classified according to American College of Rheumatology (ACR) criteria[14] and for those with microscopic polyangiitis according to the Chapel Hill consensus definition.[15] Patients not meeting these criteria were designated unclassified systemic vasculitis.

All patients were tested for anticardiolipin antibodies (aCL) and lupus anticoagulant (LA) on at least one occasion. The following information was recorded: (*a*) diagnosis; (*b*) age and sex; (*c*) aCL and LA status; (*d*) clinical features of APS (for example, thrombosis, recurrent fetal loss, florid livedo reticularis, thrombocytopenia). Patients' results were classified as follows: (*a*) *classical APS*—fully met international consensus (Sapporo) criteria for definite APS[16]; (*b*) *possible APS*—patients with positive serology (aCL and/or LA) and some clinical features of APS but not enough to fulfil the Sapporo criteria; (*c*) *positive serology only*—no clinical features but presence of aCL and/or LA; (*d*) *negative*—no features of APS; (*e*) according to the *anti-thrombotic treatment* that had been instituted (none/low dose aspirin alone/formal anticoagulation).

The aCL and LA were detected by standard methods in our laboratory.[17 18] Patients with positive aPL were classified according to the significance of these results. Those who met the international consensus criteria were classified as having definite APS. Those who had clinical features of APS with positive aCL or LA serology but not fulfilling the international criteria were classified as possible APS.

RESULTS

One hundred and forty four patients (53 male, 91 female) attending the vasculitis clinic were included in the study. Their median age was 54 years (range 18–91). Of the 144 patients, 89 were classified according to the ACR criteria and a further patient was diagnosed with microscopic polyangiitis under the Chapel Hill Consensus definition. Patients classified according to the ACR criteria included: 42 with Wegener's granulomatosis, 18 Churg-Strauss syndrome, 14 polyarteritis nodosa, 6 Henoch-Schönlein purpura, 6 giant cell arteritis, and 3 Takayasu's arteritis. Eighteen were classified clinically as follows: cutaneous vasculitis (9 patients), vasculitis of the central nervous system (3

Abbreviations: aCL, anticardiolipin antibodies; ACR, American College of Rheumatology; aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; LA, lupus anticoagulant; PSV, primary systemic vasculitis

Table 1 Summary of patients with systemic vasculitis who also had a definite (Sapporo criteria) diagnosis of antiphospholipid syndrome

1	64	M	Polyarteritis nodosa	IgA >160 U/ml multiple occasions	–	Multiple venous thrombotic events	Lifelong warfarin
2	52	F	Relapsing polychondritis	IgG >16 U/ml multiple occasions	–	Bilateral deep vein thromboses (no other cause found)	Lifelong warfarin
3	56	M	Wegener's granulomatosis	IgM up to 70 IU/ml multiple occasions	–	DVT × 1 (no other cause found)	Lifelong warfarin
4	56	F	Churg-Strauss syndrome	–	Multiple positives	Thrombotic CVA (no other cause found)	Lifelong warfarin
5	64	M	Unclassified systemic disease	IgG × 2	–	DVT and PE	Started warfarin, died on ITU
6	71	F	Giant cell arteritis (29 μ/ml, 17 μ/ml)	IgM × 2	–	Thrombotic CVA	Lifelong warfarin
7	60	F	Churg-Strauss syndrome	–	Multiple positives	Thrombotic CVA	Lifelong warfarin
8	55	M	Limited Wegener's granulomatosis	IgM > 17 U/ml	–	Thrombotic microangiopathy on renal biopsy	
9	39	F	Takayasu's disease	IgG 10.4 U/ml	Multiple positives	recurrent abortions (4) and one intrauterine death	Aspirin 75 mg daily

DVT, deep vein thrombosis; CVA, cardiovascular accident; PE, pulmonary embolism.

patients), mesenteric vasculitis (2 patients), cryoglobulinaemic vasculitis (2 patients), relapsing polychondritis (1 patient), and retinal vasculitis (1 patient). A further 36 patients with vasculitis remained unclassified.

The average age at diagnosis was 45 and the average treatment duration was 8 years. Vasculitis Damage Index (VDI) scores were available for 135/144 patients. The mean (SD) VDI at diagnosis was 2.13 (1.71) and at the last follow up was 2.72 (2.18). Of the 42 patients with Wegener's granulomatosis, half had localised and half generalised disease. Of the Wegener's group overall, 34 required treatment with cyclophosphamide at presentation while a further 3 required cyclophosphamide subsequently.

Of these 144 patients, 25 (17%) had some features of the APS: 9 (6%) had classical APS by Sapporo criteria while 4 had features of APS with positive serology but not enough for the Sapporo criteria (probable or possible APS). A further 12 had positive aPL serology with no significant clinical features; the remaining 119 were completely negative for aPL. Table 1 summarises the patients with definite APS. Of the 12 patients with positive aPL but without clinical features of APS, one had positive serology for both aCL and LA, four were positive for aCL alone, and the remaining seven were LA positive. Of the seven positive for LA alone, four were positive on multiple occasions.

DISCUSSION

Our results show a prevalence of definite APS of 6% (9/144) in our population of patients with PSV. A further 3% (4/144) have features (both clinical and serological) of APS and we have classified these as possible APS. Additionally, 8% (12/144) have positive serology for aCL or LA, or both.

As this series is retrospective it is subject to possible left censorship bias in that some patients may have died during the 12 month collection period. We made every effort to include patients who had died and although two patients did die during this period, (definite APS patient 5 and a further patient who was aPL and LA negative) this did not significantly affect our results.

The nine patients with definite APS demonstrate that the APS may occur in association with a PSV, complicating clinical management for these cases. Six of the 12 patients with serological features of APS had persistently positive serology. Of note, although Behçet's disease was included in our cohort of patients with vasculitis, none of these patients had a thrombosis or positive serology at any time.

It has been suggested that aPL are associated with acute vascular inflammation,[19] and their temporary presence in the serum is a reflection of polyclonal globulin secretion. Thus, their presence in vasculitis may simply represent a secondary response. Another hypothesis is that the endothelial cell disruption which occurs in vasculitis reveals cryptic antigens and stimulates antiendothelial cell antibodies that may be part of the spectrum of aPL.[20] In this case, aPL might just be an epiphenomenon of endothelial phospholipid exposure due to vascular inflammation, as proposed by Manna *et al*.[7] Some authors found positive aPL in patients with acute infections such as mycoplasma, adenovirus, rubella, chicken pox, and mumps.[21] The levels often declined when the infection resolved, were often low, and not associated with thrombosis. This possibility might explain the presence of aPL in some of our patients; particularly the patients with only one weak positive result. However, many of our patients had high titre positive antibody levels which were consistently present over time. Only one patient (patient No 5 with definite APS) had a well demonstrated infection at the time of aPL testing.

Our series of patients highlight the fact that some patients appear to have highly pathogenic LA or aCL and thrombosis while other patients, often with high antibody titre levels, do not. Possibly, the pathogenicity of the antibodies is influenced by host genetic factors, antibody isotype, and underlying vessel wall integrity, as proposed by Norden *et al*.[19]

In conclusion, our data suggest that aPL can be present in patients with PSV and may influence its clinical course and management. Studies are in progress to assess the possible impact of aPL on morbidity in these patients.

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REFERENCES

1 **Fernandez RLF**, Gil JG. Anticardiolipin antibodies and polyarteritis nodosa. *Lupus* 1994;**3**:523–4.

2 **Cohney S**, Saviage J, Stewart MR. Lupus anticoagulant in anti-neutrophil cytoplasmic antibody-associated polyarteritis. *Am J Nephrol* 1995;**15**:157–60.
3 **Dasgupta B**, Almond MK T. Polyarteritis nodosa and the antiphospholipid syndrome. *Br J Rheumatol* 1997;**36**:1210–12.
4 **Morelli S**, Perrone C, Paroli M. Recurrent cerebral infarctions in polyarteritis nodosa with circulating antiphospholipid antibodies and mitral valve disease. *Lupus* 1998;**7**:51–2.
5 **Handa R**, Aggarwal P, Biswas A, Wig N, Wali JP. Microscopic polyangiitis associated with antiphospholipid syndrome. *Rheumatology (Oxford)* 1999;**38**:478–9.
6 **Castellino G**, La Corte R, Santilli D, Trotta F. Wegener's granulomatosis associated with antiphospholipid syndrome. *Lupus* 2000;**9**:717–20.
7 **Manna R**, Latteri M, Cristiano G, Todaro L, Scuderi F, Gasbarrini G. Anticardiolipin antibodies in giant cell arteritis and polymyalgia rheumatica: a study of 40 cases. *Br J Rheumatol* 1998;**37**:208–10.
8 **Seriolo B**, Cutolo M, Garnero A, Accardo S. Risk factors for thrombotic events in giant cell arteritis and polymyalgia rheumatica. *Br J Rheumatol* 1998;**37**:1251–3.
9 **Ruffatti A**, Montecucco C, Volante D, Del Ross T, Sartori T, Rapizzi E, *et al*. Antiphospholipid syndrome and polymyalgia rheumatica/giant cell arteritis. *Rheumatology (Oxford)* 2000;**39**:565–7.
10 **Hull R**, Harris E, Gharavi A, Tincani A, Asherson RA, Valesini G, *et al*. Anticardiolipin antibodies: occurrence in Behçet's syndrome. *Ann Rheum Dis* 1984;**43**:746–8.
11 **Baranov A**, Kirdianov S, Nasonov E, Beketova T, Gurieva M, Bashina O, *et al*. Antibodies to anticardiolipin and β2GP1 in systemic vasculitis and primary antiphospholipid syndrome. *J Rheumatol* 2001;**28**(suppl):5(T59).
12 **Merkel P**, Chang Y, Pierangeli S, Convery K, Harris EN, Polisson RP. The prevalence and clinical associations of anticardiolipin antibodies in a large inception cohort of patients with connective tissue diseases. *Am J Med* 1996;**101**:576–83.
13 **Cervera R**, Piette JC, Font J, Khamashta MA, Shoenfeld Y, Camps MT, *et al*. Antiphospholipid syndrome. The clinical and immunogenic manifestations and patterns of disease expression in a cohort of 1,000 patients. *Arthritis Rheum* 2002;**46**:1019–27.
14 **Hunder GG**, Arend WP, Bloch DA, Calabrese LH, Fauci AS, Fries JF, *et al*. The American College of Rheumatology 1990 criteria for the classification of vasculitis:introduction. *Arthritis Rheum* 1990;**33**:1065–7.
15 **Jenette JC**, Falk RJ, Andrassy K, Bacon PA, Churg J, Gross WL, *et al*. Nomenclature of systemic vasculitidies. Proposal of an international consensus conference. *Arthritis Rheum* 1994;**37**:187–92.
16 **Wilson WA**, Gharavi AE, Koike T, Lockshin MD, Branch DW, Piette JC, *et al*. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome. *Arthritis Rheum*, 1999;**42**;1309–11..
17 **Harris EN**, Chan JKN, Asherson RA, Aber VR, Gharavi AE, Hughes GRV. Thrombosis, recurrent fetal loss and thronbocytopenia. Predictive value of the anticardiolipin antibody test. *Arch Intern Med* 1986;**146**:2153–6.
18 **Brandt JT**, Triplett DA, Alving B, Scharrer I. Criteria for the diagnosis of lupus anticoagulants: an update. *Throm Haemost* 1995;**74**:1185–90.
19 **Norden DK**, Ostrov BE, Shafritz AB, Von Feldt JM. Vasculitis associated with antiphospholipid syndrome. *Semin Arthritis Rheum* 1995;**24**:273–81.
20 **Baguley E**, Hughes GRV. Antiendothelial cell antibodies. *J Rheumatol* 1989;**16**:716–17.
21 **Vaarala O**, Palosuo T, Kleemola M, Aho K. Anticardiolipin response in acute infections. *Clin Immunol Immunopathol* 1986;**41**:8–15.

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Mortality in the Catastrophic Antiphospholipid Syndrome

Causes of Death and Prognostic Factors in a Series of 250 Patients

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Objective. **To assess the main causes of death and the prognostic factors that influence mortality in patients with the catastrophic antiphospholipid syndrome (CAPS).**

Methods. **We analyzed the case reports of 250 patients included in the CAPS Registry up to February 2005. To identify prognostic factors for CAPS, we compared the main clinical and immunologic features and the types of treatment in the patients who died with those features in the patients who survived.**

Results. **Recovery occurred in 56% of the episodes of CAPS and death occurred in 44%. Cerebral involvement, consisting mainly of stroke, cerebral hemorrhage, and encephalopathy, was considered the main cause of death, being present in 27.2% of patients, followed by cardiac involvement (19.8%) and infection (19.8%). The only factor we identified that was prognostic of a higher mortality rate was the presence of systemic lupus erythematosus (SLE). A higher recovery rate was associated with combined treatment with anticoagulants (ACs) plus corticosteroids (CS) plus plasma exchange (PE) (77.8%), followed by ACs plus CS plus PE and/or intravenous immunoglobulins (69%). In contrast, concomitant treatment with cyclophosphamide did not demonstrate additional benefit.**

Conclusion. **Cerebral involvement (mainly consisting of stroke), cardiac involvement, and infections were considered the main causes of death in patients with CAPS. The presence of SLE was related to a higher mortality rate. According to the results of the present study, ACs plus CS plus PE should be the first line of therapy in patients with CAPS.**

The "catastrophic" variant of the antiphospholipid syndrome (CAPS) was described by Asherson in 1992 (1) as a condition characterized by multiple vascular occlusive events, usually affecting the small vessels, and presenting over a short period of time, with laboratory confirmation of the presence of antiphospholipid antibodies. Several large series demonstrating an increase in the number of patients with this condition over the last few years have been reported (2,3). Due to the diversity of the clinical and serologic presentations that have been described under the term "catastrophic APS," an international consensus statement on the classification of CAPS was developed (4). In 2003, the eponym "Asherson's syndrome" was proposed for the condition (5).

The disorder is characterized by a diffuse thrombotic microvasculopathy with a predilection for the lung, brain, heart, kidney, skin, and gastrointestinal tract. In contrast to classic APS, single venous or arterial occlusions of the medium-to-large blood vessels are uncommon. However, atypical occlusive events, such as those of the adrenal, pancreatic, splenic, and testicular vessels, characterize CAPS (6).

Although patients with CAPS represent <1% of all patients with APS (7), the condition is usually life-

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threatening. The largest published series reported a mortality rate of ~50% in CAPS patients (2,3). Classically, it has been described as a syndrome that results in multiple organ failure, but the cause of the high mortality rate is still unknown. In most patients, cardiac problems seemed to be the major cause of death (e.g., myocardial microthrombi leading to cardiac failure, acute myocardial infarction, and cardiac arrest). Respiratory failure, occurring mainly as acute respiratory distress syndrome (ARDS), was also present in several of these patients (3).

In the present study, we analyzed the causes of death as well as the prognostic factors that can influence mortality in patients with CAPS.

SUBJECTS AND METHODS

We analyzed case reports that were included in the CAPS Registry, a Web-based international registry of patients with CAPS, until February 2005. This registry was recently created by the European Forum on Antiphospholipid Antibodies, a study group devoted to the development of multicenter projects with large populations of APS patients. It contains clinical, laboratory, and therapeutic data on all reported cases of CAPS. The CAPS Registry, including a complete list of members of the European Forum on Antiphospholipid Antibodies, can be freely consulted through the Internet (http://www.med.ub.es/MIMMUN/FORUM/CAPS.HTM).

The sources of information in the CAPS Registry are the personal communications of the physicians who treated these patients as well as published reports of patients with CAPS. A search of Medline for published reports in order to locate all cases of CAPS is performed periodically, using the following key words: catastrophic, antiphospholipid, catastrophic antiphospholipid syndrome. Patients who are included in the CAPS Registry fulfill the classification criteria for CAPS (4). According to these criteria, 53.8% of the patients had definite CAPS and 46.2% had probable CAPS. We summarized data from these patients using a standardized form that included sex, age, diagnosis of the underlying disorder, main clinical manifestations, immunologic features, and treatment. Clinical and immunologic characteristics of some of these patients have been previously described (2,3,8,9).

Patients who died were also analyzed separately. The clinical diagnosis considered by their physician-in-charge to be the cause of death and the findings at autopsy (when described) were evaluated. In order to identify prognostic factors in patients with CAPS, the main clinical and immunologic features and the types of treatment in the patients who died were compared with those in the patients who survived.

To assess the influence of the time of diagnosis on the evolution of CAPS, we divided the 250 patients into 2 groups according to the year their CAPS was diagnosed: 149 patients were diagnosed before 2001, and 78 patients were diagnosed between 2001 and February 2005. This information was not obtained in 23 of the 250 patients. The year 2001 was selected as the cutoff because the largest series of 80 patients with catastrophic APS was published that year (3).

Statistical analyses were performed with SPSS for Windows statistical software (version 10.0; SPSS, Chicago, IL). Values are reported as the mean ± SD. Mean values of continuous variables were compared using Student's *t*-test or the nonparametric Mann-Whitney U test. Chi-square and Fisher's exact tests were performed to evaluate differences between categorical data in patients with CAPS. Multiple logistic regression analysis was also performed. All statistical tests were 2-tailed, and only associations with a P value less than 0.05 were considered statistically significant.

RESULTS

Up to February 2005, the CAPS Registry included 250 patients. The main demographic, clinical, and laboratory features of these patients are given in Table 1. Of the 250 patients in the CAPS Registry at that time, patients 1–130 have been described in detail in previous case reviews (2,3). The main clinical characteristics, laboratory features, treatments, and outcomes in patients 131–250 are available at the CAPS Registry Web site (http://www.med.ub.es/MIMMUN/FORUM/CAPS.HTM).

Among the 250 patients, 112 (44.8%) died at the time of the CAPS event. For our analyses, each episode of CAPS was considered separately, including those in the 4 patients who had recurrences (3 patients with 2 recurrences and 1 patient with 3 recurrences). A total of 255 episodes of CAPS were analyzed.

Major causes of death and findings of histopathologic studies. The major cause of death was identified in 81 of 114 patients who died (71.1%) (Table 2). Cerebral involvement was the most frequent cause of death, being present in 22 of the 81 patients (27.2%). Cardiac involvement was identified as the major cause of death in 16 of the 81 patients (19.8%), followed by infection in 16 patients (19.8%), multiple organ failure in 14 (17.3%), pulmonary involvement in 8 (9.9%), and abdominal involvement in 4 (4.9%).

Autopsy was performed in 58 of the 114 patients (50.9%) (Table 2). The main occlusive features were microthrombosis, which was identified in 49 patients (84.5%), followed by infarcts in 31 (53.4%), thrombosis of the large vessels in 11 (19%), and pulmonary embolism in 7 (12.1%). Nonbacterial thrombotic endocarditis was identified in 16 patients (27.6%). The mitral valve was the most commonly affected, followed by the aortic and tricuspid valves.

Prognostic factors. There were no differences in distribution by sex, mean age, the presence of a precipitating factor at the time of CAPS, and the number of

Table 1. Demographic, clinical, and laboratory features of 250 patients with CAPS*

Demographics	
Sex, no. female/no. male	177/73
Age at the time of CAPS, mean ± SD years	37 ± 14
Diagnosis, no. (%) of patients	
Primary APS	116 (46.4)
SLE	100 (40)
SLE-like	12 (4.8)
Other	22 (8.8)
No. (%) with precipitating factors†	143 (56)
No. (%) with CAPS as the first manifestation of APS	116 (46.4)
Main organ involved, no. (%)†	
Kidney	180 (70.6)
Lung	163 (63.9)
Brain	158 (62)
Heart	131 (51.4)
Skin	128 (50.2)
Liver	85 (33.3)
Intestine	60 (23.5)
Peripheral veins (thrombosis)	59 (23.1)
Spleen	48 (18.8)
Adrenal gland	33 (12.9)
Peripheral arteries (thrombosis)	27 (10.6)
Pancreas	19 (7.5)
Retina	17 (6.7)
Peripheral nerve	12 (4.7)
Bone marrow	10 (3.9)
Laboratory features, no./no. tested (%)‡	
IgG aCL	197/236 (83.5)
IgM aCL	92/221 (41.6)
IgA aCL	3/71 (4.2)
Lupus anticoagulant	173/223 (77.6)
Disseminated intravascular coagulation	33/221 (14.9)
Thrombotic microangiopathic hemolytic anemia	19/221 (8.6)

* CAPS = catastrophic antiphospholipid syndrome; SLE = systemic lupus erythematosus; aCL = anticardiolipin antibodies.
† In relation to 255 episodes of CAPS.
‡ Lupus anticoagulant (LAC) was present in 173 of 223 patients tested (77.6%). In 63 patients (36.4%), the case records stressed that LAC was detected according to the guidelines of the International Society on Thrombosis and Hemostasis (Scientific Subcommittee on Lupus Anticoagulants/Phospholipid-Dependent Antibodies). In the remaining patients, the case records did not state which method was used to determine LAC.

organs affected between patients who died and those who survived (Table 3). Patients with systemic lupus erythematosus (SLE) had a higher mortality rate compared with those with primary APS (59% versus 37.9%; $P = 0.003$). However, we did not find differences in the first clinical manifestation at the time of CAPS or in CAPS as the first manifestation of APS, or in the clinical manifestations attributed to thrombotic and nonthrombotic events during the episode of CAPS (ARDS, encephalopathy, and myocardial dysfunction) between patients who died and those who survived.

There were no differences in the laboratory features, including the presence of disseminated intravascular coagulation, parameters of hemolysis, and the antiphospholipid antibody profile between patients with CAPS who died and those who survived (Table 4). Thrombocytopenia (platelet count $\leq 100{,}000/mm^3$) was more common in survivors, but the difference was not statistically significant. The presence of antinuclear antibodies was associated with an increased mortality rate (65.9% versus 49.1%; $P = 0.017$).

Table 2. Major cause of death and findings of histopathologic studies in patients with CAPS*

	No. (%) of patients with CAPS
Major cause of death (n = 81)	
Cerebral involvement	22 (27.2)
Stroke	15 (18.5)
Cerebral hemorrhage	4 (4.9)
Encephalopathy	3 (3.7)
Cardiac involvement	16 (19.8)
Cardiac failure	14 (17.3)
Arrhythmias	2 (2.5)
Infection	16 (19.8)
Bacterial sepsis	10 (12.3)
Fungal sepsis	3 (3.7)
Pneumocystis carinii pneumonia	2 (2.5)
Suppurative peritonitis	1 (1.2)
Multiple organ failure	14 (17.3)
Pulmonary involvement	8 (9.9)
Acute respiratory distress syndrome	6 (7.4)
Pulmonary embolism	1 (1.2)
Pulmonary hemorrhage	1 (1.2)
Abdominal involvement	4 (4.9)
Liver failure	3 (3.7)
Acute abdomen	1 (1.2)
Histopathologic features (n = 58)	
Microthrombosis	49 (84.5)
Kidney	32 (65.3)
Heart	27 (55.1)
Lung	24 (48.9)
Brain	24 (48.9)
Spleen	12 (24.5)
Skin	11 (22.4)
Gut	10 (20.4)
Liver	10 (20.4)
Adrenal gland	8 (16.3)
Infarction	31 (53.4)
Brain	19 (61.3)
Heart	9 (29)
Spleen	6 (19.4)
Kidney	5 (16.1)
Lung	5 (16.1)
Adrenal gland	3 (9.7)
Thrombosis of large vessels	11 (18.9)
Pulmonary embolism	7 (12.1)
Nonbacterial thrombotic endocarditis	16 (27.6)
Acute respiratory distress syndrome	4 (6.8)
Alveolar hemorrhage	3 (5.2)
Budd-Chlari syndrome	1 (1.7)
Adrenal hemorrhage	1 (1.7)

* CAPS = catastrophic antiphospholipid syndrome.

Table 3. General characteristics of, and precipitating factors in, patients with CAPS, categorized according to their death or survival*

	Patients who died during a CAPS episode (n = 112)	Patients who survived a CAPS episode (n = 138)
Age at the time of CAPS, mean ± SD years	38.5 ± 13	36.6 ± 15.2
Sex, no. female/no. male	82/30	95/43
Diagnosis, no. (%) of patients		
SLE (n = 100)	59 (59)†	41 (41)
Primary APS (n = 116)	44 (37.9)	72 (62.1)
No. (%) with precipitating factors‡	60 (52.6)	83 (59.3)
Infection	21 (18.4)	31 (21.9)
Surgery	4 (12.3)	14 (10)
Withdrawal of oral ACs/low INR	9 (7.9)	9 (6.4)
Medications	4 (3.5)	10 (7.1)
Obstetric complications	3 (2.6)	10 (7.1)
Neoplasia	12 (10.5)	7 (5)
Trauma	0	3 (2.1)
SLE flare	3 (2.6)	5 (3.5)
No. (%) with CAPS as the first manifestation of APS‡	49 (43.8)	67 (48.6)
First clinical manifestation at the time of CAPS, no. (%)‡		
Pulmonary involvement	15 (27.3)	12 (13.3)
Neurologic involvement	11 (20)	16 (17.8)
Renal involvement	6 (10.9)	16 (17.8)
Cutaneous involvement	5 (9.1)	9 (10)
Cardiac involvement	1 (1.8)	9 (10)
Adrenal involvement	0	1 (1.1)
Multiple organ failure	1 (1.8)	5 (5.6)
No. (%) with ≥3 organs affected	93 (46.5)	107 (53.5)

* CAPS = catastrophic antiphospholipid syndrome; SLE = systemic lupus erythematosus; ACs = anticoagulants; INR = international normalized ratio (for the prothrombin time).
† $P = 0.003$ versus those with a diagnosis of primary APS.
‡ In relation to episodes of CAPS.

Treatment and outcome. Data on treatment were not available in 7 patients, and in another 6 patients, none of the treatments that we analyzed was used. A total of 242 episodes of CAPS were analyzed (Table 5). Recovery occurred in 56% of CAPS episodes and death occurred in 44%.

Individual treatments. Anticoagulants (ACs) were the most frequent treatment, being used in 206 of the 242 episodes of CAPS (85.1%). Unfractionated heparin was used in 147 episodes (60.7%), low molecular weight heparin in 31 (12.8%), oral ACs in 101 (41.7%; in 28 episodes, this was the only AC treatment used), and for

Table 4. Laboratory features of patients with CAPS, categorized according to their death or survival*

	Patients who died during a CAPS episode (n = 114)	Patients who survived a CAPS episode (n = 136)
Disseminated intravascular coagulation	15/90 (16.7)	18/131 (13.7)
Hemolysis	33/101 (32.7)	42/119 (35.3)
Thrombocytopenia (≤100,000 platelets/mm^3)	34/86 (39.5)	54/101 (53.4)
Schistocytes	9/78 (11.5)	20/108 (18.5)
Antinuclear antibodies	62/94 (65.9)†	56/114 (49.1)
Antiphospholipid antibodies		
IgG aCL	87/103 (84.5)	110/133 (82.7)
IgM aCL	35/92 (38)	57/129 (44.2)
Lupus anticoagulant	78/97 (80.4)	95/126 (75.4)

* Values are the number of patients/number tested (%). CAPS = catastrophic antiphospholipid syndrome; aCL = anticardiolipin antibodies.
† $P = 0.017$ versus the group that survived.

Table 5. Treatments used during the 242 episodes of CAPS*

	No. (%) of CAPS episodes treated	No. (%) of CAPS episodes with recovery
Individual treatments		
ACs	206 (85.1)	130 (63.1)†
CS	190 (78.5)	106 (55.8)
CYC	75 (30.9)	39 (52)
PE	73 (30.1)	45 (61.6)
IVIGs	51 (21.1)	30 (58.8)
AGs	26 (10.4)	16 (61.5)
Treatment combinations		
ACs + CS	48 (19.8)	30 (63.8)
ACs + CS + PE and/or IVIGs	42 (17.4)	29 (69)
ACs alone	39 (16.1)	25 (64.1)
ACs + CS + CYC + PE and/or IVIGs	34 (14)	21 (61.8)
ACs + CS + CYC	19 (7.9)	10 (52.6)
ACs + CS + PE	18 (7.4)	14 (77.8)
ACs + CS + CYC + PE	17 (7)	11 (64.7)
ACs + CS + IVIGs	15 (6.2)	9 (60)
CS alone	11 (4.5)	2 (18.2)‡
ACs + CS + PE + IVIGs	9 (3.7)	6 (66.7)
ACs + CS + CYC + IVIGs	9 (3.7)	4 (44.4)
ACs + CS + CYC + PE + IVIGs	8 (3.3)	6 (75)
ACs + CS + AGs	6 (2.5)	3 (50)
ACs + AGs	5 (2)	4 (80)
CS + CYC + PE	5 (2)	2 (40)
CS + CYC	5 (2)	0
CS + PE	4 (1.7)	1 (25)
ACs + CS + CYC + AGs	3 (1.2)	1 (33.3)
ACs + CS + IVIGs + AGs	2 (0.8)	2 (100)
ACs + CYC + PE + IVIGs	2 (0.8)	1 (50)
ACs + PE	2 (0.8)	0
CS + CYC + AGs	2 (0.8)	1 (50)
ACs + CS + CYC + PE + AGs	1 (0.4)	1 (100)
IVIGs alone	1 (0.4)	1 (100)
ACs + CS + PE + AGs	1 (0.4)	1 (100)
ACs + CS + CYC + PE + IVIGs + AGs	1 (0.4)	1 (100)
PE + AGs	1 (0.4)	0
CS + AGs	1 (0.4)	0
CS + IVIGs	1 (0.4)	0
CS + PE + AGs	1 (0.4)	0
ACs + CYC + AGs	1 (0.4)	0
CS + CYC + PE + AGs	1 (0.4)	0
PE + IVIGs	1 (0.4)	0
CS + CYC + IVIGs	1 (0.4)	0
CS + PE + IVIGs	1 (0.4)	0

* Treatment was not recorded for 7 of the patients, and in 6 other patients, none of these treatments were given. A total of 242 episodes of catastrophic antiphospholipid syndrome (CAPS) were analyzed. ACs = anticoagulants; CS = corticosteroids; CYC = cyclophosphamide; PE = plasma exchange; IVIGs = intravenous immunoglobulins; AGs = antiaggregants (platelet aggregation inhibitors).
† $P < 0.0001$, odds ratio 5.98 (95% confidence interval 2.84–13.80) versus episodes not treated with ACs.
‡ $P = 0.01$ versus episodes not treated with CS.

the remaining episodes, heparin was the initial treatment during the acute episode, followed by oral ACs when the prothrombin time was at an international normalized ratio (INR) of 2–3.5; there were no reports of patients with a prothrombin time with an INR of <2. There was no statistically significant difference between patients who died and those who survived in relation to the types of anticoagulation treatment received.

Corticosteroids (CS) were used in 190 episodes of CAPS (78.5%) and were given as intravenous pulses (500–1,000 mg/day for 1–3 days) in 65 episodes (34.2%) and as oral or intravenous dosages of 1–2 mg/kg/day in 64 (33.7%). These data were not available in the remaining 61 episodes. Cyclophosphamide (CYC) was used in 75 episodes (30.9%) and was given as an intravenous pulse in 40 episodes (53.3%) and as an oral dose (50–100

mg/day) in 10 (13.3%). Route of administration was not specified in the remaining 25 episodes. There was no statistically significant difference between patients who died and those who survived with regard to the dosages and routes of administration of CS and CYC.

Plasma exchange (PE) was used as the treatment in 73 of the 242 episodes of CAPS (30.1%), intravenous immunoglobulins (IVIGs) were used in 51 (21.1%), and antiaggregants (AGs; platelet aggregation inhibitors) were used in 26 (10.7%).

Other treatments used were hemodialysis in 44 episodes (18.2%), antibiotics in 36 (14.9%), surgery in 15 (6.2%; including splenectomy in 3), defibrotide and prostacyclin in 3 episodes each (1.2%), cyclosporine and azathioprine in 2 episodes each (0.8%), and mycophenolate mofetil and danazol in 1 episode each (0.4%). In addition, 34 episodes (14.0%) required ventilatory support.

Considering the presence or absence of a single treatment, recovery occurred in 63.1% of the CAPS episodes treated with ACs versus 22.2% in episodes not treated with ACs ($P < 0.0001$, odds ratio [OR] 5.98 [95% confidence interval (95% CI) 2.84–13.80). In addition, for episodes treated with the following agents versus episodes not treated with that agent, recovery occurred in 55.8% with CS treatment versus 56.9%, in 52% with CYC treatment versus 57.8%, in 61.6% with PE versus 53.7%, in 58.8% with IVIGs versus 55.3%, and in 61.5% with AGs versus 56.4% (P not significant for each comparison). Moreover, hemodialysis was associated with increased mortality (61.4% in episodes requiring hemodialysis versus 37% in those that did not; $P = 0.007$).

Treatment combinations. Most patients received a combination of nonsurgical therapies (Table 5). ACs plus CS was the most common combination (19.8%), followed by ACs plus CS plus PE and/or IVIGs (17.4%). The higher recovery rate was achieved by the combination of ACs plus CS plus PE (77.8%), followed by ACs plus CS plus PE and/or IVIGs (69%), but there was no statistical difference between them. In contrast, concomitant treatment with CYC did not demonstrate additional benefit. Considering the presence and absence of a specific combination of treatments, there were no differences in the recovery rate. However, in the case of ACs plus CS plus PE and/or IVIGs and ACs plus CS plus PE, there was a trend toward a higher rate of recovery for episodes that were treated with this combination versus those that were not (69% versus 54.4% [$P = 0.089$], and 77.8% versus 55.4% [$P = 0.083$], respectively). Treatment with CYC did not demonstrate an additional benefit. In addition, we found that the isolated use of CS was related to a lower rate of recovery (18.2% versus 58.1% of episodes not treated with CS; $P = 0.01$).

Time of diagnosis and outcome. To assess the influence of the time of diagnosis on outcome in the CAPS patients, we categorized the 250 patients into 2 groups according to the year CAPS was diagnosed. One hundred forty-nine patients were diagnosed before 2001, and 78 patients from 2001 to February 2005. This information could not be obtained in 23 patients (Table 6).

The mortality rate decreased over time, from 53% in those diagnosed before 2001 (first period) to 33.3% in those diagnosed between 2001 and February 2005 (second period) ($P = 0.005$, OR 2.25 [95% CI 1.27–3.99]). In order to investigate the causes of this decrease in the mortality rate, we compared the characteristics between these 2 groups. There were no differences in distribution by sex, diagnosis, CAPS as the first manifestation of APS, the first clinical manifestation at the time of catastrophic APS, and the number of organs affected. Patients diagnosed in the second period were younger than those diagnosed in the first period (34.4 ± 11.8 years versus 39.4 ± 14.8 years; $P = 0.016$). In addition, a higher number of precipitating factors for CAPS episodes was identified in the second period as compared with the first period ($P = 0.017$).

When we analyzed the treatments that were used during each period, we found no differences in the use of specific treatments according to the year of diagnosis. However, when we compared the combination of treatments that achieved a higher recovery rate in the entire series, we found that in patients with CAPS diagnosed in the second period, the combination of ACs plus CS plus PE and/or IVIGs was used more often than in the group with CAPS diagnosed in the first period (28.6% versus 13.3%; $P = 0.007$, OR 2.61 [95% CI 1.30–5.21]). In addition, this treatment combination was used most often for CAPS episodes diagnosed in the second period. In contrast, treatment combinations that included CYC were used less often in the second period than in the first period.

Using logistic regression analysis that included age, the presence of a precipitating factor, and the rate of use of combined therapy with ACs plus CS plus PE and/or IVIGs, the decrease in mortality rates seen during the second period was associated with the mean age at the time of CAPS ($P = 0.039$, OR 0.97 [95% CI 0.95–0.99]) and with the higher rate of use of combined therapy with ACs plus CS plus PE and/or IVIGs ($P = 0.025$, OR 2.26 [95% CI 1.10–4.62]).

Table 6. Outcome in patients with CAPS, categorized according to year of diagnosis*

	CAPS diagnosis before 2001	CAPS diagnosis between 2001 and February 2005
No. (%) of patients who died	79 (53)	26 (33.3)†
Age at the time of CAPS, mean ± SD years	39.4 ± 14.8	34.4 ± 11.8‡
Sex, no. female/no. male	105/44	55/22
Diagnosis, no. (%) of patients		
SLE	52 (36.9)	36 (47.4)
Primary APS	69 (48.9)	34 (44.7)
No. (%) with precipitating factors§	74 (50)	52 (66.7)¶
CAPS as the first manifestation of APS§	67 (45.9)	32 (41.6)
First clinical manifestation at the time of CAPS§		
Neurologic involvement	20 (20.8)	7 (16.3)
Renal involvement	15 (15.6)	7 (16.3)
Pulmonary involvement	20 (20.8)	5 (11.6)
Cardiac involvement	5 (5.2)	5 (11.6)
Cutaneous involvement	9 (9.4)	3 (7)
Multiple organ involvement, no. (%) of patients		
3 organs affected	32 (21.4)	22 (28.2)
4 organs affected	31 (20.8)	16 (20.5)
5 organs affected	32 (21.4)	17 (21.8)
6 organs affected	14 (9.4)	5 (6.4)
Individual treatments, no. (%) of CAPS episodes#		
ACs	110 (76.9)	68 (88.3)
CS	105 (73.4)	65 (84.4)
CYC	45 (31.5)	18 (23.4)
PE	45 (31.5)	26 (33.8)
IVIGs	25 (17.5)	21 (27.3)
AGs	13 (9.1)	8 (10.4)
Treatment combinations, no. (%) of CAPS episodes#		
ACs + CS (n = 43)	25 (17.5)	18 (23.4)
ACs alone (n = 33)	27 (18.9)	6 (7.8)**
ACs + CS + PE (n = 18)	9 (6.3)	9 (11.7)
ACs + CS + CYC + PE (n = 16)	11 (7.7)	5 (6.5)
ACs + CS + IVIGs (n = 14)	7 (4.9)	7 (9.1)
ACs + CS + PE + IVIGs (n = 9)	3 (2.1)	6 (7.8)
ACs + CS + PE and/or IVIGs (n = 41)	19 (13.3)	22 (28.6)††
ACs + CS + CYC + PE and/or IVIGs (n = 31)	22 (15.4)	9 (11.7)

* CAPS = catastrophic antiphospholipid syndrome; SLE = systemic lupus erythematosus; ACs = anticoagulants; CS = corticosteroids; CYC = cyclophosphamide; PE = plasma exchange; IVIGs = intravenous immunoglobulins; AGs = antiaggregants (platelet aggregation inhibitors).
† $P = 0.005$, odds ratio 2.25 (95% confidence interval 1.27–3.99) versus patients with CAPS diagnosed before 2001.
‡ $P = 0.016$ versus patients with CAPS diagnosed before 2001.
§ In relation to episodes of CAPS.
¶ $P = 0.017$ versus patients with CAPS diagnosed before 2001.
# The total number of CAPS episodes treated before 2001 was 143; the total treated between 2001 and February 2005 was 77.
** $P = 0.03$ versus patients with CAPS diagnosed before 2001.
†† $P = 0.007$, odds ratio 2.61 (95% confidence interval 1.30–5.21) versus patients with CAPS diagnosed before 2001.

DISCUSSION

The outcome of patients with CAPS in the present series was similar to outcomes reported in 1998 and 2001 (2,3), with a marginal reduction in the mortality rate, from 50% to 45.6%. The present study was a retrospective analysis that was performed with information provided by physicians-in-charge and gathered from published case reports. There have been no prospective randomized trials of patients with CAPS; however, because of the rarity and severity of CAPS, such trials would be quite difficult to perform. Although the data from the present study should be considered with caution, the CAPS Registry has proved to be a useful tool, and several important conclusions can be drawn from our findings.

First, the presence of SLE was related to a higher mortality rate in patients with CAPS. The association of antinuclear antibody positivity with an increased mortality rate can be explained by the coexistence of SLE in these patients. Second, we confirmed the lower mortality rate associated with the use of AC therapy (36.9% versus 77.8%; $P < 0.0001$), which was demonstrated in the series reported in 2001 (3). In addition, the use of ACs for the treatment of CAPS increased from 70% in the 1998 series (2) to 84% in the 2001 series (3) and to 85.1% in the present series. When we analyzed the diverse combinations of treatments, ACs plus CS was the most common combination, followed by ACs plus CS plus PE and/or IVIGs, which was used in almost 40% of the CAPS episodes. The higher rate of recovery was achieved by the combination of ACs plus CS plus PE (77.8%), followed by ACs plus CS plus PE and/or IVIGs (69%). In contrast, the addition of CYC did not demonstrate any further benefit. Although there were no differences in the recovery rate with regard to the presence or absence of a specific treatment combination, in the case of the combination ACs plus CS plus PE and/or IVIGs and the combination ACs plus CS plus PE, there was a trend toward a higher rate of recovery for CAPS episodes that were treated with these combinations versus those that were not (69% versus 54.4% [$P = 0.089$] and 77.8% versus 55.4% [$P = 0.083$], respectively). In contrast, we found that the isolated use of CS had a poorer prognosis ($P = 0.01$).

Another point of interest of our study is the analysis of the influence of the time of CAPS diagnosis on these prognostic factors. We demonstrated that the episodes of CAPS that were diagnosed, and therefore treated, from 2001 to February 2005 had a higher recovery rate compared with those diagnosed and treated before 2001. We believe that the difference in the mean age at the time of CAPS diagnosis between the first and second periods, although statistically significant, was not high enough to explain the decreased mortality rate for those diagnosed during the second period. Episodes of CAPS diagnosed during the second period showed a higher number of precipitating factors. This fact may indicate that physicians are increasingly recognizing CAPS, and therefore, earlier and more specific treatment for both the precipitating factors and CAPS is being prescribed. However, we believe that the main explanation for this significant reduction in mortality rates was the increased use of combined treatment with ACs plus CS plus PE and/or IVIGs.

In this regard, combination therapy with ACs plus CS plus PE and/or IVIGs was the most commonly used treatment for CAPS cases diagnosed from 2001 to February 2005. This is consistent with the international consensus guidelines for the management of CAPS (4). If CAPS is suspected, aggressive treatment is required without delay. General measures, such as treatment or elimination of precipitating factors, should be applied in addition to first-line therapies (ACs with intravenous heparin plus high doses of CS). Second-line therapies (IVIGs and/or PE) are necessary in the absence of a clinical response or when the condition is life-threatening (vital organ involvement and development of organ failure). In the case of a deteriorating clinical situation, one of the third-line treatments (CYC, fibrinolytics, ancrod, defibrotide, prostacyclin, and anticytokine therapies) should be considered, although experience with these treatments in CAPS is very limited and/or the effects on outcome are unknown. The results of the present study reinforce this treatment strategy. Furthermore, Uthman et al (10) also recommended the inclusion of CAPS in the category II or III indications for therapeutic PE.

With regard to clinical diagnosis of the causes of death in these patients with CAPS, cerebral involvement was considered the main cause of death, being present in 27.1% of patients, mainly consisting of stroke. However, cardiac and pulmonary conditions together represented the main cause of death, being present in 29.6% of patients, which is consistent with the rates in previously published series (2,3).

The main finding of autopsy was microthrombosis, which was present in 84.5% of patients. This is one of the features that differentiate classic APS from catastrophic APS. In the former, single venous or arterial occlusions of the medium-to-large blood vessels usually dominate the clinical picture. In CAPS, however, severe multiple organ dysfunction, characterized by diffuse small-vessel ischemia and thromboses predominantly affecting the parenchymal organs, dominates (11,12). CAPS is associated with endothelial cell activation as a result of antigen–antibody reactions on the surface of endothelial cells or monocytes. The activation of endothelial cells and the accompanying up-regulation of adhesion molecules and tissue factor are likely to be pivotal to the development of CAPS. The clinical manifestations of CAPS depend on (a) the organs that are affected by the thrombotic events and the extent of the thrombosis, as well as (b) manifestations of the systemic inflammatory response syndrome (SIRS), which are presumed to be due to excessive release of cytokines from affected and necrotic tissues (13). It is now recognized that SIRS may arise both from sepsis and from

noninfectious causes, such as immune-mediated organ injury. ARDS (14), encephalopathy (15), and myocardial dysfunction (16) are the clinical manifestations that have been related to the development of SIRS.

In conclusion, the only identified prognostic factor for a higher mortality rate in patients with CAPS was the presence of SLE. According to the results of the present study, we advocate the use of a combined treatment with ACs plus CS plus PE as first-line therapy in patients with CAPS. The higher rate of the use of combination treatment with ACs plus CS plus PE and/or IVIGs seems to be the main explanation for the significant reduction in mortality rates that we found in CAPS episodes diagnosed during the period from 2001 to February 2005. Further prospective studies using large-scale registries such as the CAPS Registry will help us to better assess the prognostic factors and appropriate treatment of patients with CAPS.

REFERENCES

1. Asherson RA. The catastrophic antiphospholipid syndrome. J Rheumatol 1992;19:508–12.
2. Asherson RA, Cervera R, Piette JC, Font J, Lie JT, Burcoglu A, et al. Catastrophic antiphospholipid syndrome: clinical and laboratory features of 50 patients. Medicine (Baltimore) 1998;77: 195–207.
3. Asherson RA, Cervera R, Piette JC, Shoenfeld Y, Espinosa G, Petri MA, et al. Catastrophic antiphospholipid syndrome: clues to the pathogenesis from a series of 80 patients. Medicine (Baltimore) 2001;80:355–76.
4. Asherson RA, Cervera R, de Groot PG, Erkan D, Boffa MC, Piette JC, et al. Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines. Lupus 2003;12:530–4.
5. Piette JC, Cervera R, Levy RA, Nasonov EL, Triplett DA, Shoenfeld Y. The catastrophic antiphospholipid syndrome—Asherson's syndrome. Ann Med Interne (Paris) 2003;154:195–6.
6. Asherson RA. The catastrophic antiphospholipid (Asherson's) syndrome in 2004. Autoimmun Rev 2005;4:48–54.
7. Cervera R, Piette JC, Font J, Khamashta MA, Shoenfeld Y, Camps MT, et al, and the Euro-Phospholipid Project Group. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthritis Rheum 2002;46:1019–27.
8. Erkan D, Cervera R, Asherson RA. Catastrophic antiphospholipid syndrome: where do we stand? [review]. Arthritis Rheum 2003;48: 3320–7.
9. Erkan D, Asherson RA, Espinosa G, Cervera R, Font J, Piette JC, et al. Long term outcome of catastrophic antiphospholipid syndrome survivors. Ann Rheum Dis 2003;62:530–3.
10. Uthman I, Shamseddine A, Taher A. The role of therapeutic plasma exchange in the catastrophic antiphospholipid syndrome. Transfus Apher Sci 2005;33:11–7.
11. Harris EN, Pierangeli S. Primary, secondary, catastrophic antiphospholipid syndrome: is there a difference? Thromb Res 2004;114:357–61.
12. Meroni PL, Raschi E, Camera M, Testoni C, Nicoletti F, Tincani A, et al. Endothelial activation by aPL: a potential pathogenetic mechanism for the clinical manifestations of the syndrome. J Autoimmun 2000;15:237–40.
13. Burcoglu-O'ral A, Erkan D, Asherson RA. Treatment of catastrophic antiphospholipid syndrome (CAPS) with defibrotide, a proposed vascular endothelial cell modulator. J Rheumatol 2002; 29:2006–11.
14. Bhatia M, Moochhala S. Role of inflammatory mediators in the pathophysiology of acute respiratory distress syndrome. J Pathol 2004;202:145–56.
15. Bolton CF. Sepsis and the systemic inflammatory response syndrome: neuromuscular manifestations. Crit Care Med 1996;24: 1408–16.
16. Ren J, Wu S. A burning issue: do sepsis and systemic inflammatory response syndrome (SIRS) directly contribute to cardiac dysfunction? Front Biosci 2006;11:15–22.

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Laboratory studies on pathophysiology of the catastrophic antiphospholipid syndrome

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Abstract

The 'catastrophic' variant of the antiphospholipid syndrome (APS) is characterized by a diffuse thrombotic microvasculopathy. In contrast to the classical APS, single venous or arterial medium-to-large blood vessel occlusions are uncommon. The mechanisms of catastrophic APS are not clearly understood. In addition, there are no studies on pathophysiologic mechanisms of catastrophic APS.

The clinical manifestations of catastrophic APS probably depend on (a) the organs affected by the thrombotic events and extent of the thrombosis and (b) manifestations of the systemic inflammatory response syndrome which are presumed to be due to excessive cytokine release from affected and necrotic tissues.

The evident relationship between APS and infection may enable us to explain the development of catastrophic APS using the sepsis model. This is because catastrophic APS is characterized by multiple microvascular thrombotic events, of rapid onset, and causing multiorgan failure, a picture suggestive of septic shock, in which, there is a massive, acute inflammatory response.

Keywords: Catastrophic APS; Pathogenesis; Systemic inflammatory distress syndrome; Multiorgan dysfunction syndrome; Thrombotic microangioapathy

Contents

1. Introduction

The 'catastrophic' variant of the antiphospholipid syndrome (APS) was described by Asherson in 1992 [1] as a condition characterized by multiple vascular occlusive events, usually affecting small vessels, presenting over a short period of time, and laboratory confirmation of the presence of antiphospholipid antibodies (aPL). Several large series have been reported demonstrating an increase in the number of patients with this condition over the past few years [2,3]. Due to the

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diversity of the clinical and serological presentations that have been published under this term, an international consensus on classification for catastrophic APS has been developed [4]. In 2003, the eponym "Asherson's Syndrome" was attached to the condition [5]

The disorder is characterized by a diffuse thrombotic microvasculopathy with a predilection for lung, brain, heart, kidney, skin, and gastrointestinal tract. In contrast to the classical APS, single venous or arterial medium-to-large blood vessel occlusions are uncommon. However, atypical occlusive events involving adrenal, pancreatic, splenic, and testicular vessels characterize the catastrophic APS [6].

Although patients with catastrophic APS represent less than 1% of all patients with APS [7], they are usually in a life-threatening situation. In this respect, the mortality rate is around 50% in the largest published series [2,3]. Classically, it has been described as a syndrome resulting in multiorgan failure but the cause of this high mortality is still unknown. In most patients, cardiac problems seemed to be the major cause of death (e.g. myocardial microthrombi, leading to cardiac failure, acute myocardial infarction and cardiac arrest). Respiratory failure, mainly as acute respiratory distress syndrome (ARDS), was also present in several of these patients [3].

The main finding of necropsy studies was microthrombosis, present in 84.5% of patients. This is one of the features that differentiates classic APS from catastrophic APS. In the former, single venous or arterial medium-to-large blood vessel occlusions usually dominate the clinical picture. In catastrophic APS, however, severe multiple organ dysfunction characterized by diffuse small vessel ischemia and thromboses predominantly affecting the parenchymal organs dominates the clinical picture [8].

2. Pathophysiologic mechanisms

The mechanisms of catastrophic APS are not clearly understood. It is still unclear as to why some patients will develop recurrent thromboses, mainly affecting large vessels, while others develop rapidly recurrent vascular occlusions, predominantly affecting small vessels. Indeed, the preceding precipitating or "trigger" factors may be identical in either simple or classic APS patients and in those with catastrophic APS. Clearly, other factors, as yet unidentified, must play important roles.

The pathogenesis of catastrophic APS has not received as much attention as have the clinical manifestations. The rarity of the condition, its high mortality, sporadic cases only encountered in many different geographical areas and hospitals, and lack of education of intensive care units physicians have undoubtedly led to difficulties in collecting blood and serum samples from affected patients both during the episode, and if they survive, later as well.

The clinical manifestations of catastrophic APS probably depend on (a) the organs affected by the thrombotic events and extent of the thrombosis and (b) manifestations of the systemic inflammatory response syndrome (SIRS) which are presumed to be due to excessive cytokine release from affected and necrotic tissues. At present, these two explanations remain theoretical.

It is now recognized that SIRS may arise both from sepsis and from non-infectious causes, such as immune-mediated organ injury. The acute respiratory distress syndrome (ARDS) [9], encephalopathy [10] and myocardial dysfunction [11], clinical manifestations present in patients with catastrophic APS, have all been related with the development of SIRS.

The hypothesis advanced by Kitchens is significant in the pathogenesis of this condition in selected patients [12]. Of the 6 patients he reported as suffering with what he termed "thrombotic storm", 3 were clear examples of catastrophic APS, and, although antiphospholipid antibody tests were not performed in the remainder, it is highly probable that these were also examples of the condition. He hypothesized that the newly formed clots in some patients with preexisting hypercoagulability continued to provide thrombin formation. Fibrinolysis is secondarily depressed by the increase in plasminogen activator inhibitors referred to as fibrinolytic "shut down", and coagulation activation products, viz. prothrombin activation product F1 and 2, thrombin antithrombin complexes, and protein C-activated peptide, are elevated simultaneously. There may be a reduction in the natural anticoagulant proteins such as antithrombin, protein C, protein S, and also β_2 glycoprotein I (GPI).

It can be seen that 60% of patients appear to have developed catastrophic APS following an identifiable "trigger" factor, with infections dominating the list [13]. Postulated mechanisms by which infections may cause thrombosis have been a subject of much interest over the past 5 years. Asherson and Shoenfeld proposed a theory of "molecular mimicry" in 2000 [14].

The sepsis response begins with the activation of host cells by recognition of lipopolysaccharide (LPS). The main mechanism by which LPS is sensed is via an LPS-binding protein (LBP) and then signaling through the Toll-like receptor 4 (TLR4). TLRs are a key component of the innate immune response able to recognize specific microbial products including LPS. Intracellular signaling depends on binding of the intracellular TLR domain to IRAK (IL-1 receptor-associated kinase), a process that is facilitated by an adapter protein MyD88 (myeloid

differentiation protein 88). The activation of IRAK induces the nuclear translocation of nuclear factor-κβ (NF-κβ) and ultimately the activation of cytokine gene promoters such as IL-1, IL-6, and TNF-α [15].

In vitro activation of endothelial cells mediated by anti-β_2GPI antibodies was found to be associated with NF-κB translocation from the cytoplasm to the nucleus [16]. However, the upstream signalling steps have been only recently investigated. Both human monoclonal IgM as well as polyclonal IgG anti-β_2GPI antibodies trigger an endothelial signalling cascade comparable to that activated by LPS and MyD88 [17]. Anti-β_2GPI antibodies and LPS induce a comparable phosphorylation of the IRAK. These findings raised the possibility that the autoantibodies activate endothelial cells through the TLR-4 involved in LPS pathway [17].

Anti-β_2GPI antibodies were shown to recognize β_2GPI peptides displaying a molecular mimicry with common bacteria and viruses, both at the level of amino acid sequence and conformational structure [18]. Such a homology was suggested to represent the rationale for the possible infectious origin of the syndrome. Because common microbial structures do represent the natural ligand for TLRs, it has been speculated that β_2GPI might interact with TLRs and that anti-β_2GPI antibodies recognizing the molecule might cross-link it together with TLRs eventually triggering the inflammatory cascade.

Since these receptors are intimately involved with innate immunity directed especially towards infections as prevalent as "triggering" factors in catastrophic APS, their role remains to be further explored and studies looking at differing phenotypes in those patients manifesting catastrophic APS are needed.

Another point of interest is the presence of thrombotic microangiopathy as a hallmark of catastrophic APS. Thrombotic microangiopathies (TMA) are a group of entities characterized by the presence of schistocytic hemolysis and consumptive thrombocytopenia and which include thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome (HUS), HELLP syndrome, malignant hypertension, scleroderma renal crisis, disseminated cancer, human immunodeficiency virus infection, and may be precipitated by some drugs such as cyclosporyne A, ticlopidine, and clopidogrel [19]. The presence of schistocytes in catastrophic APS makes the differential diagnosis between catastrophic APS and TTP difficult in aPL patients with predominantly renal and neurological involvement. There remains a possibility that, pathologically, catastrophic APS and TTP might be a partially identical syndrome, and some cases of catastrophic APS may be diagnosed as TTP or vice versa.

Classic idiopathic TTP result from severe deficiency of the metalloprotease enzyme ADAMTS13, which prevents microvascular platelet aggregation by the cleaving of the adhesive von Willebrand factor (vWF) secreted by endothelial cells. This gives rise to unusually large multimers of circulating vWF, which react with platelet glycoprotein, triggering pathologic aggregation of platelets at intravascular sites. Hereditary TTP is caused by homozygous or double heterozygous ADAMTS13 mutations. Acquired TTP is usually associated with autoantibodies against ADAMTS13.

What then does the current research in ADAMTS13 deficiency in APS show? Amoura et al. described 2 patients with TTP and primary APS [20]. In the same work, these authors described the results of tests for ADAMTS13 activity in 20 patients with primary APS, as well as tests for aPL in 26 patients who had TTP with severe ADAMTS13 deficiency and ADAMTS13 inhibiting antibodies. In both patients with TTP and primary APS, ADAMTS13 activity was undetectable and ADAMTS13 inhibiting antibodies were present. In 20 patients with primary APS, no severe deficiency of ADAMTS13 was observed. Finally, only 1 of the 26 patients with TTP had a low level of IgG anticardiolipin antibodies (aCL). Moreover, Rieger et al. studied the prevalence of ADAMTS13 antibodies in 59 patients with TMA, 40 patients with systemic lupus erythematosus (SLE) and 55 patients with APS [21]. In patients with acute acquired TMA and plasma levels of ADAMTS13 activity below 10%, IgG antibodies against ADAMTS13 were found in 97% and IgM antibodies in 11%. In contrast, anti-ADAMTS13 IgG or IgM antibodies were detected in only 20% of patients with TMA with ADAMTS13 activity above 10%. Patients with SLE and APS had prevalences of IgG antibodies of 13% and 5%, respectively. A high prevalence of anti-ADAMTS13 IgM antibodies was found in patients with SLE and APS (18% each), but the clinical significance of these IgM antibodies in these groups is unclear. However, all these evidences suggest that ADAMTS13 deficiency may play a role in some cases of catastrophic APS.

3. Future research

The most important future objective is to collect blood and serum samples from patients with catastrophic APS, especially during acute episodes. This will permit laboratory studies on the pathophysiology of catastrophic APS, including the cytokine profile, anti-β2GPI antibody specificity, complement deficiencies, TLRs and mannose-binding lectin polymorphisms, and the possible role of ADAMTS13 deficiency. Hopefully, this will lead to improved management of these patients.

Take-home messages

- In catastrophic APS, severe multiple organ dysfunction characterized by diffuse small vessel ischemia and thromboses predominantly affecting the parenchymal organs dominates the clinical picture.
- The mechanisms of catastrophic APS are not clearly understood. What is left at present are hypotheses based on extrapolations of studies on classic APS.
- The clinical manifestations of catastrophic APS probably depend on the organs affected by the thrombotic events and extent of the thrombosis and the manifestations of the SIRS. The ARDS, encephalopathy and myocardial dysfunction, clinical manifestations present in patients with catastrophic APS, have all been related with the development of SIRS.
- There is some evidence that anti-β2GPI antibodies trigger an endothelial signalling cascade comparable to that activated by LPS. Thus, anti-β2GPI antibodies might link to TLRs, triggering the inflammatory cascade. This seems likely to play a major role in catastrophic APS.
- There is some evidence that catastrophic APS induced by anti-β2GPI antibodies share with the sepsis response the increased expression of tissue factor and PAI-1 on endothelial cells and monocytes, and the role of complement activation.
- The ADAMTS13 deficiency may play a role in some cases of catastrophic APS.

References

[1] Asherson RA. The catastrophic antiphospholipid syndrome. J Rheumatol 1992;19:508–12.

[2] Asherson RA, Cervera R, Piette JC, et al. Catastrophic antiphospholipid syndrome: clinical and laboratory features of 50 patients. Medicine (Baltimore) 1998;77:195–207.

[3] Asherson RA, Cervera R, Piette JC, et al. Catastrophic antiphospholipid syndrome: clues to the pathogenesis from a series of 80 patients. Medicine (Baltimore) 2001;80:355–76.

[4] Asherson RA, Cervera R, de Groot PR, et al. Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines. Lupus 2003;12: 530–4.

[5] Piette JC, Cervera R, Levy RA, et al. The catastrophic antiphospholipid syndrome-Asherson's syndrome. Ann Med Interne (Paris) 2003;154:195–6.

[6] Asherson RA. The catastrophic antiphospholipid (Asherson's) syndrome in 2004. Autoimmu Rev 2005;4:48–54.

[7] Cervera R, Piette JC, Font J, et al. Antiphospholipid syndrome: clinical and immnologic manifestations and patterns of disease expression in a cohort of 1000 patients. Arthritis Rheum 2002;46:1019–27.

[8] Meroni PL, Raschi E, Camera M, et al. Endothelial activation by aPL: a potential pathogenetic mechanism for the clinical manifestations of the syndrome. J Autoimmun 2000;15:237–40.

[9] Bhatia M, Moochhala S. Role of inflammatory mediators in the pathophysiology of acute respiratory distress syndrome. J Pathol 2004;202:145–56.

[10] Bolton CF. Sepsis and the systemic inflammatory response syndrome: neuromuscular manifestations. Crit Care Med 1996;24: 1408–16.

[11] Ren J, Wu S. A burning issue: do sepsis and systemic inflammatory response syndrome (SIRS) directly contribute to cardiac dysfunction? Front Biosci 2006;11:15–22.

[12] Kitchens CS. Thrombotic storm: when thrombosis begets thrombosis. Am J Med 1998;104:381–5.

[13] Asherson RA. Multiorgan failure and antiphospholipid antibodies: the catastrophic antiphospholipid (Asherson's) syndrome. Immunobiology 2005;210:727–33.

[14] Asherson RA, Shoenfeld Y. The role of infection in the pathogenesis of catastrophic antiphospholipid syndrome. Molecular mimicry? J Rheumatol 2000;27:12–4.

[15] Cohen J. The immunopathogenesis of sepsis. Nature 2002;420: 885–91.

[16] Meroni PL, Raschi E, Testoni C, et al. Statins prevent endothelial cell activation induced by antiphospholipid (anti-β_2 glycoprotein I) antibodies. Arthritis Rheum 2001;44:2870–8.

[17] Raschi E, Testoni C, Bossio D, et al. Role of MyD88 transduction signaling pathway in endothelial activation by antiphospholipid antibodies. Blood 2003;101:3495–500.

[18] Blank M, Asherson RA, Cervera R, et al. Antiphospholipid syndrome infectious origin. J Clin Immunol 2004;24:12–23.

[19] Lämmle B, Kremer Hovinga JA, Alberio L. Thrombotic thrombocytopenic purpura. J Thromb Haemost 2005;3:1663–75.

[20] Amoura Z, Costedoat-Chalumeau N, Veyradier A, et al. Thrombotic thrombocytopenic purpura with severe ADAMTS-13 deficiency in two patients with primary antiphospholipid syndrome. Arthritis Rheum 2004;50:3260–4.

[21] Rieger M, Manucci PM, Kremer Hovinga JA, et al. ADAMTS13 autoantibodies in patients with thrombotic microangiopathies and other immunomediated diseases. Blood 2005;106:1262–7.

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Mortality in the catastrophic antiphospholipid syndrome: Causes of death and prognostic factors

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Abstract

In order to know the causes of death and the prognostic factors, our group analyzed 250 patients included until February 2005 in the web-site based international registry of patients with catastrophic antiphosphopholipid syndrome (APS) ("CAPS Registry") (http://www.med.ub.es/MIMMUN/FORUM/CAPS.HTM). Cerebral involvement, mainly consisting of stroke, followed by cardiac involvement and infections were considered the main causes of death in patients with catastrophic APS. The presence of systemic lupus erythematosus was related with higher mortality. According to the results of this analysis, anticoagulation plus steroids plus plasma exchange should be the first line of therapy in patients with catastrophic APS.

Contents

1. Introduction

The 'catastrophic' variant of the antiphospholipid syndrome (APS) was described by Asherson in 1992 [1] as a condition characterized by multiple vascular occlusive events, usually affecting small vessels, presenting over a short period of time, and laboratory confirmation of the presence of antiphosphoplipid antibodies (aPL). Several large series have been reported demonstrating an increase in the number of patients with this condition over the past few years [2,3].

Although patients with catastrophic APS represent less than 1% of all patients with APS [4], they are

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Table 1
Causes of death and necropsy finding in patients who died with catastrophic APS

Total of patients who died	46% (114/250)
Clinical diagnosis of death	71.7% (81/114)
Cerebral involvement	19.5% (22/114)
Stroke	13.3% (15/114)
Cerebral haemorrhage	3.5% (4/114)
Encephalopathy	2.7% (3/114)
Cardiac involvement	14.1% (16/114)
Cardiac failure	12.2% (14/114)
Arrhytmias	1.8% (2/114)
Infection	14.1% (16/114)
Bacterial sepsis	8.8% (10/114)
Sepsis by candida	2.6% (3/114)
Cerebral abscesses	0.9% (1/114)
Pneumocistis carinii	1.8% (2/114)
Multiorgan failure	12.4% (14/114)
Pulmonary involvement	7.1% (8/114)
ARDS	5.3% (6/114)
Pulmonary embolism	0.9% (1/114)
Pulmonary haemorrhage	0.9% (1/114)
Abdominal involvement	4.5% (5/114)
Liver failure	2.7% (3/114)
Acute abdomen	1.8% (2/114)
Necropsy	52.2% (59/114)

usually in a life-threatening situation. In this respect, the mortality rate is around 50% in the largest published series [2,3]. Classically, it has been described as a syndrome resulting in multiorgan failure [5] but the cause of this high mortality is still unknown.

In order to know the causes of death and the prognostic factors, our group analyzed the case reports included in the web-site based international registry of patients with catastrophic APS ("CAPS Registry") [6]. This registry has been recently created by the European Forum on Antiphospholipid Antibodies, a study group devoted to the development of multicenter projects with large populations of APS patients. It contains clinical, laboratory, and therapeutic data on all reported cases of catastrophic APS, and it can be freely consulted through the Internet (http://www.med.ub.es/MIMMUN/FORUM/CAPS.HTM). Currently, it contains information on 250 patients. Among them, 112 (44.8%) died at the time of the catastrophic APS event.

2. Major cause of death

We selected those patients who died and analyzed their clinical diagnosis considered by their physician-in-charge as cause of the death and the necropsy characteristics when they were described (Table 1).

With regard to clinical diagnosis of death, cerebral involvement was considered the main cause of death, mainly consisting of stroke, followed by cardiac involvement and infection.

The main finding at necropsy studies was microthrombosis, present in 89% of patients. This is one of the features that differentiate classic APS from catastrophic APS (Table 2). In the former, single venous or arterial medium-to-large blood vessel occlusions usually dominate the clinical picture.

3. Prognostic factors

In order to identify prognostic factors in patients with catastrophic APS, we compared the main clinical and immunologic features, and the types of treatment that were used in the patients who died with those in the patients who survived.

The presence of systemic lupus erythematosus and positive antinuclear antibody titre were related with a higher mortality in patients with catastrophic APS. However, the association of positive antinuclear antibody with an increased mortality can be explained by the coexistence in these patients of systemic lupus erythematosus.

4. Treatment and outcome

We confirmed the lower mortality (36.9% versus 77.8%; $p<0.0001$) that is associated with the use of

Table 2
Necropsy finding in patients who died with catastrophic APS

Microthrombosis	89% (53/59)
Renal	62% (37/59)
Cerebral	50.8% (30/59)
Pulmonary	45.7% (27/59)
Cardiac	45.7% (27/59)
Intestinal	30.5% (18/59)
Splenic	28.8% (17/59)
Hepatic	20.3% (12/59)
Cutaneous	20.3% (12/59)
Others	35.5%..(21/59)
Infarcts	54.2% (32/59)
Cerebral	33.8% (20/59)
Myocardial	20.3% (12/59)
Splenic	10.2% (6/59)
Renal	8.4% (5/59)
Hepatic	3.3%..(2/59)
Other	11.25 (7/59)
Other findings at necropsy	
Libman Sacks endocarditis	27.1% (16/59)
Pulmonary embolism	16.9% (10/59)
Infection	10.2% (6/59)
Acute respiratory distress syndrome	6.8% (4/59)
Alveolar haemorrhage	5% (3/59)
Budd Chiari	1.6% (1/59)

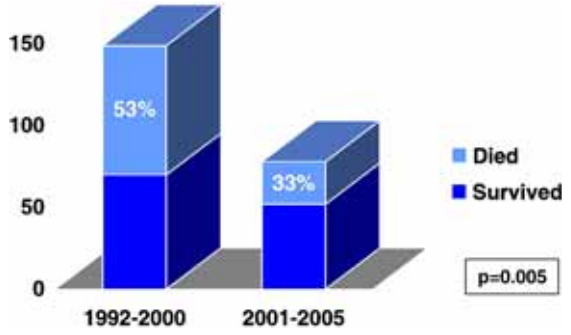

Fig. 1. Influence of the time of diagnosis on evolution in patients with catastrophic APS. The mortality decreased from 53% in the first period (1992–2000) to 33% in the second period (2001–2005). The patients with catastrophic APS diagnosed and treated after 2001 had a higher recovery rate with a statistically significant reduction on mortality of 20%.

anticoagulation (AC) as it was demonstrated in a previous study from our group [3].

When we analyzed the diverse combinations of treatments, AC+corticoids (CS) was the most common combination of treatment, followed by AC+CS+plasma exchange (PE) and/or intravenous immunoglobulins (IVIG), used in almost 40% of the patients. The higher recovery rate was achieved by the combination of AC+CS+PE (77.8%), followed by AC+CS+PE and/or IVIG (69%). In contrast, the addition of cyclophosphamide did not demonstrate any additional benefit.

5. Time of diagnosis

To assess the influence of the time of diagnosis on their evolution, we divided the 250 patients into two groups according to their year of diagnosis: 149 patients were diagnosed before 2000, and 78 patients from 2001 to February 2005. In 23 patients, this information was not obtained. The year 2001 was selected as cut-off because the largest series of 80 patients with catastrophic APS was published this year [3].

We demonstrated that the episodes of catastrophic APS diagnosed and, therefore, treated from 2001 to February 2005 had a higher recovery rate compared with those diagnosed and treated before 2001 (Fig. 1).

We consider that the difference, although statistically significant, in the mean age at the time of catastrophic APS between patients of the first and the second period is not high enough to explain the decrease of mortality rate in the second period. However, we consider that the main reason to explain this significant reduction of mortality was the higher use rate of treatments with AC+CS+PE and/or IVIG. In this sense, the combination of therapy with AC+CS+PE and/or IVIG was the most commonly used treatment in cases of catastrophic APS diagnosed from 2001.

6. Conclusion

The only identified prognostic factor for higher mortality rate in patients with catastrophic APS was the presence of systemic lupus erythematosus. According to the results of the present study, we advocate the use of a combined treatment of AC+CS+PE as a first line of therapy in catastrophic APS. The higher use rate of combined treatments with AC+CS+PE and/or IVIG seems to be the main reason to explain the significant reduction of mortality that we found in catastrophic APS episodes diagnosed from 2001.

Further prospective studies, using large-scale registries, such as the “CAPS Registry”, will help us to better assess the prognostic factors and appropriate treatment of patients with catastrophic APS.

Take-home messages

- Cerebral involvement followed by cardiac involvement and infections were the most common causes of death.
- Systemic lupus erythematosus was associated with a higher mortality rate.
- The higher recovery rate was achieved by the combination of anticoagulation (AC) plus corticoids (CS) plus plasma exchange (PE) followed by AC+CS+PE and/or intravenous immunoglobulins (IVIG).
- The addition of cyclophosphamide did not demonstrate any additional benefit.
- The mortality rate decreased 20% after the year 2001.
- The higher use rate of combined treatment with AC+CS+PE and/or IVIG was the main reason for explaining such an important reduction of mortality in patients with catastrophic APS after 2001.

References

[1] Asherson RA. The catastrophic antiphospholipid syndrome. J Rheumatol 1992;19:508–12.
[2] Asherson RA, Cervera R, Piette JC, Font J, Lie JT, Burcoglu A, et al. Catastrophic antiphospholipid syndrome: clinical and laboratory features of 50 patients. Medicine (Baltimore) 1998;77:195–207.
[3] Asherson RA, Cervera R, Piette JC, Shoenfeld Y, Espinosa G, Petri MA, et al. Catastrophic antiphospholipid syndrome: clues to the pathogenesis from a series of 80 patients. Medicine (Baltimore) 2001;80:355–76.
[4] Cervera R, Piette JC, Font J, Khamashta MA, Shoenfeld Y, Camps MT, et al. Antiphospholipid syndrome: clinical and immunologic

manifestations and patterns of disease expression in a cohort of 1000 patients. Arthritis Rheum 2002;46:1019–27.
[5] Asherson RA, Cervera R, de Groot PR, Erkan D, Boffa MC, Piette JC, et al. Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines. Lupus 2003;12:530–4.
[6] Bucciarelli S, Espinosa G, Cervera R, Erkan D, Gómez-Puerta JA, Ramos-Casals M, et al. Mortality in catastrophic antiphospholipid syndrome: causes of death and prognostic factors in a series of 250 patients. Arthritis Rheum (in press).

Anti-endothelial cell antibodies and antiphospholipid antibodies in Takayasu's arteritis: correlations of their titers and isotype distributions with disease activity

To investigate the prevalence of anti-endothelial cell antibodies (AECA) and antiphospholipid antibodies, and the correlations of their titers with disease activity in patients with Takayasu's arteritis (TA). Forty-seven patients with TA and 30 age-and sex-matched controls were studied by Park MC. et. al. (Clin Exp Rheumatol 2006; 24 (2 Suppl 41): S10-6). Blood samples were obtained from all patients and they were divided into either active or stable disease groups. Paired samples were available in 18 patients at both active and stable stage, respectively. AECA against human umbilical vein endothelial cells and antiphospholipid antibodies were measured. Forty-two (89.4%) TA patients had AECA, and positivity rates of IgM and IgG AECA were 83% and 68.1%, respectively, while those for controls were both 3.3%. The titers of IgM and IgG AECA in patients were significantly higher than in controls. IgM AECA titers of the active group were significantly higher than those of the stable group, but IgG AECA titers were not. Antiphospholipid antibodies were detected in only 4 patients with TA, but not in controls. Thus, IgM and IgG AECA were more prevalent and their titers were higher in patients with TA than in controls, and IgM AECA titers correlated well with the disease activity of TA. Antiphospholipid antibodies were not found significant.

Activation of transforming growth factor-beta 1 and early atherosclerosis in systemic lupus erythematosus

The efficiency of activating latent transforming growth factor (TGF)-beta 1 in systemic lupus erythematosus (SLE) may control the balance between inflammation and fibrosis, modulating the disease phenotype. To test this hypothesis, Jackson M. et. al. (Arthritis Research 8(3): R81) studied the ability to activate TGF-beta1 in SLE patients and control individuals within the context of inflammatory disease activity, cumulative organ damage and early atherosclerosis. An activation index (AI) for TGF-beta 1 was determined for 32 patients with SLE and 33 age-matched and sex-matched control individuals by quantifying the increase in active TGF-beta 1 under controlled standard conditions. Apoptosis in peripheral blood mononuclear cells was determined by fluorescence-activated cell sorting. Carotid artery intima-media thickness (IMT) was measured using standard Doppler ultrasound. Both IMT and TGF-beta 1 AI for SLE patients were within the normal range. There was a significant inverse association between TGF-beta 1 AI and levels of apoptosis in peripheral blood mononuclear cells after 24 hours in culture for both SLE patients and control individuals. Only in SLE patients was there a significant negative correlation between TGF-beta 1 AI and low-density lipoprotein cholesterol ($r = -0.404$; $P = 0.022$) and between TGF-beta 1 AI and carotid artery IMT ($r = -0.587$; $P = 0.0004$). A low AI was associated with irreversible damage, and was inversely correlated with disease duration. To conclude, in SLE low normal TGF-beta1 activation was linked with increased lymphocyte apoptosis, irreversible organ damage, disease duration, calculated low-density lipoprotein levels and increased carotid IMT.

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Lessons from the catastrophic antiphospholipid syndrome (CAPS) registry

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Abstract

Although less than 1% of patients with the antiphospholipid syndrome (APS) develop the catastrophic variant, its potentially lethal outcome emphasizes its importance in clinical medicine today. However, the rarity of this variant makes it extraordinarily difficult to study in any systematic way. In order to put together all the published case reports as well as the new diagnosed cases from all over the world, an international registry of patients with catastrophic APS ("CAPS Registry") was created in 2000 by the *European Forum on Antiphospholipid Antibodies*. Currently, it documents the entire clinical, laboratory and therapeutic data of more than 300 patients whose data has been fully registered. This registry can be freely consulted at the Internet (www.med.ub.es/MIMMUN/FORUM/CAPS.HTM) and it is expected that the periodical analysis of these data will allow us to increase our knowledge of this condition.

Keywords: Catastrophic antiphospholipid syndrome; Antiphospholipid antibodies; Anticardiolipin antibodies; Lupus anticoagulant; Antiphospholipid syndrome

Contents

1. Introduction

In the 1980s and early 1990s, isolated case reports appeared in the world literature documenting patients who suffered from an often fatal complication associated with the demonstration of antiphospholipid antibodies

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(aPL). The clinical picture comprised widespread multi-organ thrombosis and consequent organ failure and was referred to by the authors as a "devastating non-inflammatory vasculopathy" [1], "occlusive vasculopathy" [2] or "acute disseminated coagulopathy–vasculopathy" [3] when describing individual cases. In 1992, 10 patients with this unusual condition were first reviewed and, in an attempt to define its acuteness and severity, the adjective "catastrophic" was attached to this variant of the antiphospholipid syndrome (APS) [4].

Although less than 1% of patients with the APS develop this complication [5], its potentially lethal outcome, despite all recommended therapies, emphasizes its importance in clinical medicine today and, although many publications have drawn attention to its existence, it seems clear that many more cases still remain undiagnosed and inadequately treated in hospital settings the world over. The majority of these patients end up in intensive care units (ICU) with multi-organ failure and, unless the condition is considered in the differential diagnosis by the attending physicians, it may be completely missed with a disastrous outcome for the patients [6,7].

2. CAPS Registry

The rarity of the syndrome made it extraordinarily difficult to study in any systematic way. In order to put together all the published case reports as well as the new diagnosed cases from all over the world, an international registry of patients with catastrophic APS ("CAPS Registry") was created in 2000 by the *European Forum on Antiphospholipid Antibodies*, a study group devoted to the development of multicentre projects with large populations of APS patients.

Ricard Cervera, Jean-Charles Piette, Yehuda Shoenfeld, Josep Font, Silvia Bucciarelli and Ronald A. Asherson are the main coordinators of the "CAPS Registry". It documents the entire clinical, laboratory and therapeutic data of all published cases with catastrophic APS as well as of many additional patients whose data has been fully registered. The sources of information are the personal communications of the physicians who treated these patients and the periodically computer-assisted search of the medical literature (Medline, National Library of Medicine, Bethesda, MD) to locate all cases of published reports in English, Spanish, French, German and Italian of patients with catastrophic APS (keywords: catastrophic, antiphospholipid, catastrophic antiphospholipid syndrome).

This registry can be freely consulted through the Internet at: www.med.ub.es/MIMMUN/FORUM/CAPS.HTM. Currently, it documents the clinical, laboratory and therapeutic data of more than 300 patients whose data has been fully registered.

3. Main results

The initial results of the project have been already published in several original papers that provide information on the long-term outcome of patients with this syndrome [8], the characteristics of associated thrombotic microangiopathic hemolytic anemia [9], disseminated intravascular coagulation [10], acute respiratory distress syndrome [11], and causes of death and prognostic factors [12].

Additionally, the heterogeneity of the different clinical forms of presentation of the catastrophic APS led to the necessity of developing a consensus criteria for definition and classification of patients with this condition. In September of 2002, a pre-symposium workshop in the "Tenth International Congress on aPL" held in Taormina, Italy, allowed the establishment of preliminary criteria for the classification of catastrophic APS by using the data from the "CAPS Registry" [13] (Table 1). This

Table 1
Preliminary criteria for the classification of catastrophic APS

1. Evidence of involvement of three or more organs, systems and/or tissues[a]
2. Development of manifestations simultaneously or in less than a week
3. Confirmation by histopathology of small vessel occlusion in at least one organ or tissue[b]
4. Laboratory confirmation of the presence of antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies)[c]

Definite catastrophic APS: all four criteria.
Probable catastrophic APS: all four criteria, except for only two organs, systems and/or tissues involvement; all four criteria, except for the absence of laboratory confirmation at least 6 weeks apart due to the early death of a patient never previously tested for aPL prior to the catastrophic APS event; 1, 2 and 4; 1, 3 and 4 and the development of a third event in more than a week but less than a month, despite anticoagulation.

[a] Usually, clinical evidence of vessel occlusions, confirmed by imaging techniques when appropriate. Renal involvement is defined by a 50% rise in serum creatinine, severe systemic hypertension (>180/100 mm Hg) and/or proteinuria (>500 mg/24 h).

[b] For histopathological confirmation, significant evidence of thrombosis must be present, although vasculitis may coexist occasionally.

[c] If the patient had not been previously diagnosed as having an APS, the laboratory confirmation requires that presence of antiphospholipid antibodies must be detected on two or more occasions at least 6 weeks apart (not necessarily at the time of the event), according to the proposed preliminary criteria for the classification of definite APS [9].

consensus statement is of major importance, as patients with a debatable diagnosis or with less severe disease ("probable" catastrophic APS) may now be classified separately and distinctly from those with a "definite" catastrophic APS. From the analysis of the initial 176 patients included in the "CAPS Registry" [14], 89 (51%) of the previously compiled patients with catastrophic APS were classified as having "definite" and 70 (40%) as "probable" catastrophic APS. The sensitivity of these criteria was 90.3% and the specificity 99.4%. Positive and negative predictive values were 99.4% and 91.1%, respectively. These criteria will now provide a more consistent diagnostic paradigm and will assist in planning and documenting future multicentre studies.

Furthermore, the analysis of the "CAPS Registry" also allowed the establishment of an international consensus statement on treatment guidelines [13] (Fig. 1). The recent analysis of 250 patients from the registry has confirmed that the higher recovery rate was achieved by the combination of anticoagulation + corticosteroids + plasma exchange (77.8%) [12], as proposed in these guidelines.

4. Conclusion

The "CAPS Registry" has proved to be a useful tool for the study of this variant of the APS and it is expected that the periodical analysis of these data will allow us to increase our knowledge of this condition in the near future.

Take-home messages

- The rarity of the catastrophic antiphospholipid syndrome (less than 1% of patients with the antiphospholipid syndrome develop this complication) made it extraordinarily difficult to study in any systematic way.
- In order to put together all the published case reports as well as the new diagnosed cases from all over the

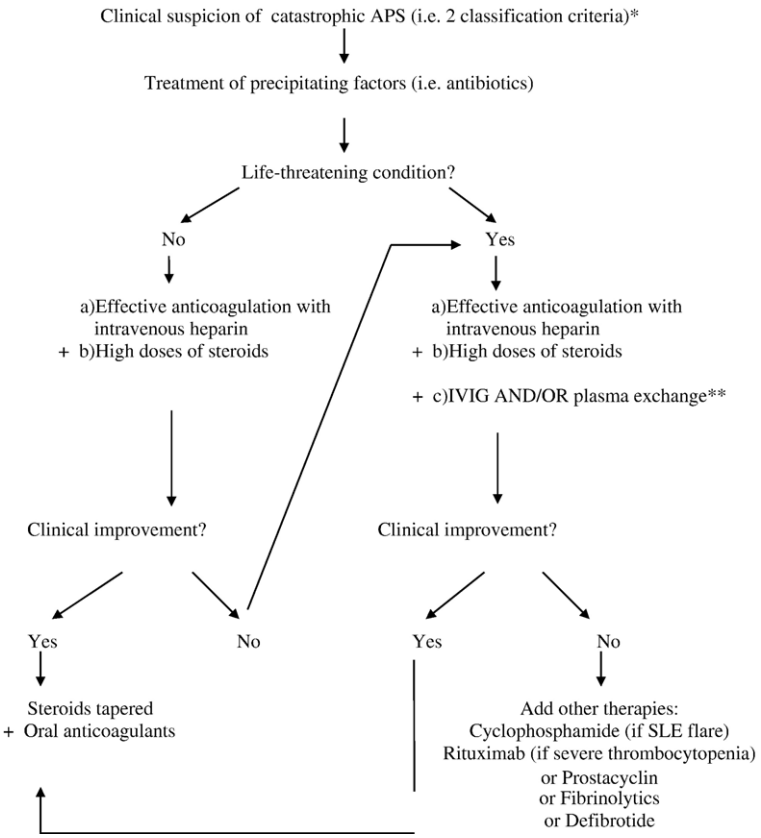

Fig. 1. Treatment algorithm of catastrophic APS. *Consider exclusion of other microangiopathic syndromes (mainly thrombotic thrombocytopenic purpura and heparin-induced thrombosis/thrombocytopenia). **With fresh frozen plasma and specially indicated if schistocytes are present.

world, an international registry of patients with catastrophic antiphospholipid syndrome ("CAPS Registry") was created in 2000.
- This registry can be freely consulted through the Internet at: www.med.ub.es/MIMMUN/FORUM/CAPS.HTM.
- The analysis of the initial 176 patients included in the "CAPS Registry" allowed the establishment of preliminary criteria for the classification of catastrophic antiphospholipid syndrome.
- Furthermore, the analysis of the "CAPS Registry" also allowed the establishment of an international consensus statement on treatment guidelines.
- The "CAPS Registry" has proved to be a useful tool for the study of this variant of the antiphospholipid syndrome and it is expected that the periodical analysis of these data will allow us to increase our knowledge of this condition in the near future.

References

[1] Ingram SB, Goodnight SH, Bennet RN. An unusual syndrome of a devastating non-inflammatory vasculopathy associated to anticardiolipin antibodies. Report of two cases. Arthritis Rheum 1987;30:1167–71.
[2] Greisman SG, Thayaparan R-S, Godwin TA, Lockshin MD. Occlusive vasculopathy in systemic lupus erythematosus—association with anticardiolipin antibody. Arch Intern Med 1991;151:389–92.
[3] Harris EN, Bos K. An acute disseminated coagulopathy–vasculopathy associated with the antiphopholipid syndrome. Arch Intern Med 1991;151:231–2.
[4] Asherson RA. The catastrophic antiphospholipid antibody syndrome. J Rheumatol 1992;19:508–12.
[5] Cervera R, Piette JC, Font J, Khamashta MA, Shoenfeld Y, Camps MT, et al. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthritis Rheum 2002;46:1019–27.
[6] Asherson RA, Cervera R, Piette JC, Font J, Lie JT, Borcoglu A, et al. Catastrophic antiphospholipid syndrome. Clinical and laboratory features of 50 patients. Medicine (Baltimore) 1998;77:195–207.
[7] Asherson RA, Cervera R, Piette JC, Shoenfeld Y, Espinosa G, Petri MA, et al. Catastrophic antiphospholipid syndrome: clues to the pathogenesis from a series of 80 patients. Medicine (Baltimore) 2001;80:355–76.
[8] Erkan D, Asherson RA, Espinosa G, Cervera R, Font J, Piette JC, et al. Catastrophic antiphospholipid syndrome registry project group. The long-term outcome of catastrophic antiphospholipid syndrome survivors. Ann Rheum Dis 2003;62:530–3.
[9] Espinosa G, Bucciarelli S, Cervera R, Lozano M, Reverter JC, De la Red G, et al. Thrombotic microangiopathic haemolytic anaemia and antiphospholipid antibodies. Ann Rheum Dis 2004;63:730–6.
[10] Asherson RA, et al, for the catastrophic antiphospholipid syndrome registry project group. Disseminated intravascular coagulation in catastrophic antiphospholipid syndrome: clinical and haematological characteristics of 23 patients. Ann Rheum Dis 2005;64:943–6.
[11] Bucciarelli S, et al, for the catastrophic antiphospholipid syndrome registry project group. The acute respiratory distress syndrome in catastrophic antiphospholipid syndrome: analysis of a series of 47 patients. Ann Rheum Dis 2006;65:81–6.
[12] Bucciarelli S, Espinosa G, Cervera R, Erkan D, Gómez-Puerta JA, Ramos-Casals M, Font J, Asherson RA for the Catastrophic Antiphospholipid Syndrome Registry Project Group. Mortality in the catastrophic antiphospholipid syndrome: Causes of death and prognostic factors in a series of 250 patients. Arthritis Rheum (in press).
[13] Asherson RA, Cervera R, de Groot P, Erkan D, Boffa MC, Piette JC, et al. Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines. Lupus 2003;12:530–4.
[14] Cervera R, et al, for the catastrophic antiphospholipid syndrome registry project group. Validation of the preliminary criteria for the classification of catastrophic antiphospholipid syndrome. Ann Rheum Dis 2005;64:1205–9.

Monoclonal anti-dsDNA antibodies cross-react with phosphoglycerate kinase 1 and inhibit the expression and production of IL-2 in activated Jurkat T cell line

The role of anti-dsDNA antibodies in tissue damage mechanism remains unclear. In this study, Luan HY. et. al. (Clin Immunol 2006; 120: 326-34) identified a 45-kDa cognate antigen of anti-dsDNA monoclonal antibodies 9D7 by two-dimensional gel electrophoresisand which determined to be human phosphoglycerate kinase 1(PGK-1) by MALDI-TOF analysis. The binding of 9D7 to PGK-1 was not affected by DNase I but was inhibited by thymus dsDNA. Human SLE sera with high anti-dsDNA titers had a high affinity with PGK. In activated Jurkat T cells, 9D7 decreased the PGK-1 mRNA production and IL-2 promoter activity. Reduction in IL-2 gene expression and protein production were observed in the 9D7-treated cells. Because PGK-1 deficiency may cause mental tardy and hemolytic anemia, interaction between anti-dsDNA and PGK-1 may be important in lupus pathogenesis. Moreover, reduction in IL-2 production by anti-dsDNA suggests their role in increasing infection rate and decreasing proper generation of activation-induced cell death.

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Pregnancy and puerperium are high susceptibility periods for the development of catastrophic antiphospholipid syndrome

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Abstract

It is well known that antiphospholipid syndrome (APS) is associated with recurrent pregnancies losses, but is also associated with other obstetric features such as preeclampsia, uteroplacental insufficiency and preterm birth. Pregnancy is a hypercoagulable state than can be complicated by thrombosis, especially in those patients with an underlying thrombophilic disorder. Catastrophic APS is a rare form of presentation of the APS. Several trigger factors have been related with the catastrophic APS, including infections, anticoagulation withdrawal, surgery, neoplasms and lupus "flares". In around 6% of the cases, the catastrophic APS can appear during pregnancy or puerperium. We review this specific subset of the catastrophic APS and propose a therapeutical approach for this particular situation.

Keywords: Antiphospholipid syndrome; Catastrophic antiphospholipid syndrome; Pregnancy losses; Pregnancy; Puerperium; Obstetric period

Contents

1. Introduction

The antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterized by a combination of arterial and/or venous thrombosis, pregnancy morbidity, often accompanied by a mild-to-moderate thrombocytopenia, and elevated titres of antiphospholipid

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antibodies (aPL), namely, the lupus anticoagulant (LA) and/or anticardiolipin antibodies (aCL) [1].

The most characteristic feature of the obstetric APS is pregnancy loss. Currently, recurrent pregnancy loss is a potentially treatable condition when it is associated with aPL [1,2]. Additionally, a wide number of other serious obstetric complications have been related with the APS, including preeclampsia, fetal growth restriction, uteroplacental insufficiency, fetal distress and medically induced preterm delivery [3]. Recently, Chakravarty et al. [4] estimated the rates of pregnancy outcomes in different autoimmune diseases, including systemic lupus erythematosus, rheumatoid arthritis and APS. Based on data from the Nationwide Inpatient Sample in US, the authors estimated that women with APS had increased risk of hypertensive disorders [OR 1.6 (1.3–2.0)], intrauterine growth restriction [OR 3.4 (2.4–4.9)] and cesarean delivery [OR 1.9 (1.6–2.2)] in comparison with healthy pregnant controls [4].

The catastrophic APS (also known as "Asherson's syndrome") is an unusual (<1%) but often life-threatening variant of the APS, characterized by the rapid appearance of multiple thromboses (mainly small vessel thrombosis) that lead to multiorgan failure [5]. Since the first description in 1992 [1], several large series have been published [6,7] and more than 250 patients have been collected in the international registry for catastrophic APS ("CAPS Registry"). It is known that catastrophic events may be triggered, in around 50% of patients, by a recognized factor, mainly infections, trauma or surgery, anticoagulation withdrawal, malignancies, lupus "flares" or, infrequently, appear during pregnancy or puerperium (i.e., after a cesarean section or fetal loss). Catastrophic APS develops during obstetric period (pregnancy or puerperium) in around 6% of the cases (Fig. 1), representing a life-threatening situation with a high mortality rate in these young women of childbearing age.

2. Pregnancy as hypercoagulable state

Pregnancy is a well-recognized hypercoagulable state that encompasses a period of 10 to 11 months (including puerperium). This hypercoagulability is explained by many factors, including abnormalities in coagulation proteins (increased levels of factors II, V, VII, VIII, X and XII as well as von Willebrand factor and decreased levels of protein S and activated protein C), abnormalities in the fibrinolytic system (low plasma fibrinolytic activity during pregnancy, labour and delivery) with a decrease activity of tissue plasminogen activator (Fig. 2) [8,9]. The presence of microparticles derived from maternal endothelial cells, platelets and placental trophoblasts also may contribute to the procoagulant situation [6]. The risk of venous thrombosis is five- to six-fold higher during pregnancy than in non-pregnant women of similar age [9]. Women with previous deep vein thrombosis (DVT) have an approximately 3.5-fold increased risk of recurrent DVT during pregnancy compared to non-pregnant periods [10].

Heit et al. [11] performed a very interesting study on the incidence of DVT and/or pulmonary embolism (PE), during pregnancy and puerperium during a long-term period of follow-up (30 years). One hundred and five cases of DVT and PE were found over 50,000 pregnancies that occurred in the studied population. The authors estimated that patients during pregnancy and puerperium had four-fold risk for the development of venous thromboembolism (VTE) than non-pregnant women of the same age. The overall incidence of VTE was higher in the postpartum periods than during pregnancy. The highest incidence of VTE during pregnancy occurred within the youngest age group (15 to 19 years), whilst during the postpartum period the incidence was higher in the oldest age group (35 years or older). The authors also estimated that the relative risk for VTE was more than five times higher during the first

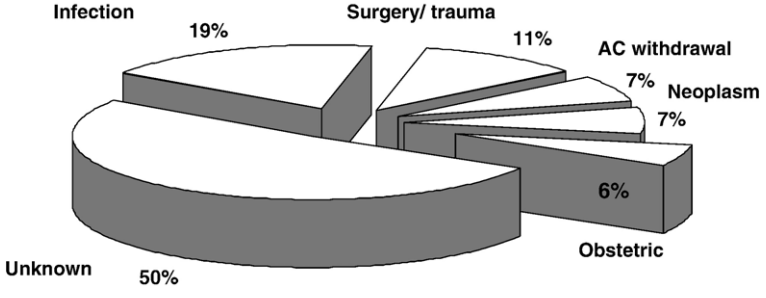

Fig. 1. Catastrophic antiphospholipid syndrome triggers. Data from Cervera R, Gómez-Puerta JA, Espinosa G et al. Ann Rheum Dis 2003;62:S75. AC: anticoagulation.

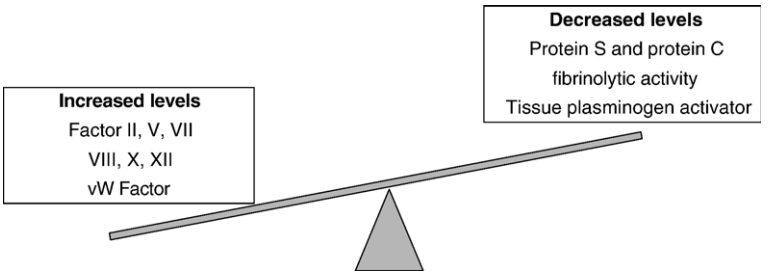

Fig. 2. Abnormalities in coagulation during pregnancy and puerperium. VW factor: von Willebrand factor proteins.

3 postpartum months versus during pregnancy [5.33 (CI, 3.55–8.02), $p<0.001$)].

Thrombophilic disorders markedly increase gestational vascular complications, leading to preeclampsia, fetal growth retardation, abruptio placentae, placental thrombosis and recurrent pregnancies losses. The different thrombophilic disorders related with recurrent pregnancy losses are collected in Table 1. Routine assessment for a thrombophilia is not currently recommended in healthy pregnant women. It is only indicated in those women with previous thrombosis and/or recurrent pregnancy losses [12].

Severe decrease in ADAMTS-13 (a von Willebrand factor-cleaving protease) activity has been recently related with thrombotic thrombocytopenic purpura (TTP) [13]. Recent studies have also evaluated ADAMTS-13 activity in pregnant women. Sanchez-Luceros et al. [14] studied ADAMTS-13 activity in a cohort of 270 healthy women (220 pregnant and 68 during puerperium). The ADAMTS-13 activity decreased progressively during pregnancy, from 12th week to the end of the postnatal period (the lowest activity was between 36 and 40 weeks and the puerperium). According to these data, the authors suggested that there is a special susceptibility for the development of thrombosis during this period.

3. Catastrophic APS during pregnancy and puerperium

There are around 15 cases of catastrophic APS that presented during pregnancy and puerperium ("CAPS Registry", 2006). Most patients had an unsuccessfully previous obstetric history (previous abortions or no previous pregnancies). Almost half of the patients presented during pregnancy (between 18 and 38 weeks) and the remaining of patients during the puerperium (from few days to 3 weeks after delivery) or after a curettage for fetal death. The main clinical thrombotic characteristics of these patients did not differ from non-pregnant patients with catastrophic APS. Multiorgan involvement with renal, pulmonary, cerebral and intraabdominal thromboses were the most common features. However, there were some particular manifestations, such as HELLP syndrome, placental thrombosis, myometrium thrombotic microangiopathy (TMA) or pelvic vein thrombosis. HELLP syndrome was severe (less than 50,000 platelets) in almost all cases. Additionally, their clinical courses were unusual in some cases, including persistent thrombocytopenia or early onset HELLP syndrome (during the second trimester).

Therapeutic strategies depend on fetal maturation and the presence of any microangiopathic feature. When pulmonary fetal maturation is ready (generally after 28th week), a prompt delivery is recommended. Plasma exchange sessions are strongly indicated in those patients with HELLP syndrome in the setting of catastrophic APS. In those cases with preclampsia or eclampsia, antihypertensive and anticonvulsivant drugs are also needed. Prevention of other potential trigger factors, mainly infections such as endometritis, cesarean wound and episiotomy wound infection, are also important. Finally, it is necessary to follow the therapeutic measures recommended in previous guidelines for the treatment of catastrophic APS [15], including steroids, anticoagulation and intravenous immunoglobulins. In spite of this aggressive treatment, mortality is still high in this particular group of patients, not only for the mothers, but also for babies.

4. Summary

Catastrophic APS during pregnancy or puerperium represents almost 6% of all cases described with

Table 1
Thrombophilic disorders associated with recurrent pregnancy losses

Antiphospholipid syndrome
Antithrombin deficiency
Factor V Leiden
Hyperhomocysteinemia
Homozygous MTHFR C677T
Protein C deficiency
Protein S deficiency
Prothrombin gene mutation

catastrophic APS. The obstetric period is a prothrombotic state and represents a unique scenario where many factors may participate as additional potential trigger factors for a catastrophic APS event, including infections, lupus flares and anticoagulation withdrawal during labour, among others.

Some specific features are seen in these patients, including HELLP syndrome, placental, pelvic vein thrombosis and myometrium TMA. Regarding treatment, it is necessary to evaluate fetus maturation and the presence of microangiopathic features. It is important to consider the possibility of the development of catastrophic APS in those patients with features of thrombotic microangiopathy (with or without HELLP syndrome) and/or multiorgan failure during pregnancy or puerperium, particularly in those patients with a previous history of abortions and/or thrombosis.

Take-home messages

- Pregnancy and puerperium periods are transient hypercoagulable states that predispose for the development of thrombosis, especially in those patients with an underlying susceptibility such as antiphospholipid syndrome (APS).
- APS is associated with several obstetric complications such as recurrent pregnancy losses, preeclampsia, fetal growth restriction, uteroplacental insufficiency, fetal distress and preterm delivery.
- In around 6% of the cases, the catastrophic APS can appear during pregnancy or puerperium.
- Patients that develop the catastrophic APS during pregnancy or puerperium have some particular manifestations, such as HELLP syndrome, placental thrombosis, myometrium thrombotic microangiopathy or pelvic vein thrombosis.
- The management of the catastrophic APS during pregnancy depends on fetal maturation and the presence of any microangiopathic feature.

References

[1] Cervera R, Piette JC, Font J, Khamashta MA, Shoenfeld Y, Camps MT, et al. Euro-phospholipid project group. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthritis Rheum 2002;46:1019–27.

[2] Cervera R, Balasch J. The management of pregnant patients with antiphospholipid syndrome. Lupus 2004;13:683–7.

[3] Branch DW, Khamashta MA. Antiphospholipid syndrome: obstetric diagnosis, management, and controversies. Obstet Gynecol 2003;101:1333–44.

[4] Chakravarty EF, Nelson L, Krishnan E. Obstetric hospitalizations in the United States for women with systemic lupus erythematosus and rheumatoid arthritis. Arthritis Rheum 2006;54:899–907.

[5] Asherson RA. The catastrophic antiphospholipid syndrome. J Rheumatol 1992;19:508–12.

[6] Asherson RA, Cervera R, Piette JC, Font J, Lie JT, Borcoglu A, et al. Catastrophic antiphospholipid syndrome. Clinical and laboratory features of 50 patients. Medicine (Baltimore) 1998;77:195–207.

[7] Asherson RA, Cervera R, Piette JC, Shoenfeld Y, Espinosa G, Petri MA, et al. Catastrophic antiphospholipid syndrome: clues to the pathogenesis from a series of 80 patients. Medicine (Baltimore) 2001;80:355–77.

[8] Brenner B. Haemostatic changes in pregnancy. Thromb Res 2004;114:409–14.

[9] Toglia MR, Weg JG. Venous thromboembolism during pregnancy. N Engl J Med 1996;335:108–14.

[10] Pabinger I, Grafenhofer H. Thrombosis during pregnancy: risk factors, diagnosis and treatment. Pathophysiol Haemost Thromb 2002;32:322–4.

[11] Heit JA, Kobbervig CE, James AH, Petterson TM, Bailey KR, Melton III LJ. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. Ann Intern Med 2005;143:697–706.

[12] Kujovich JL. Thrombophilia and pregnancy complications. Am J Obstet Gynecol 2004;191:412–24.

[13] Furlan M, Robles R, Galbusera M, Remuzzi G, Kyrle PA, Brenner B, et al. von Villebrand factor-cleaving protease in thrombotic thrombocytopenic purpura and the haemolytic-uremic syndrome. N Engl J Med 1998;339:1578–84.

[14] Sanchez-Luceros A, Farias CE, Amaral MM, Kempfer AC, Votta R, Marchese C, et al. von Willebrand factor-cleaving protease (ADAMTS13) activity in normal non-pregnant women, pregnant and post-delivery women. Thromb Haemost 2004;92:1320–6.

[15] Asherson RA, Cervera R, de Groot PG, Erkan D, Boffa MC, Piette JC, et al. Catastrophic antiphospholipid syndrome registry project group. Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines. Lupus 2003;12: 530–4.

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Review

The catastrophic antiphospholipid (Asherson's) syndrome and malignancies

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Abstract

The catastrophic antiphospholipid syndrome is characterised by the rapid chronological development of fulminant thrombotic complications that predominantly affect small vessels. It has been reported as frequently occurring in patients with underlying malignancies. We analysed the web site-based international registry of patients with catastrophic APS. The clinical characteristics of patients with CAPS and an underlying malignancy were evaluated. Of the 262 patients included in the CAPS registry, information on associated malignancies was available in 23 (9%) cases. Haematological malignancies were present in 6 (26%) patients. Four of the patients suffered from lung carcinoma (17%), and two patients (9%) from colon carcinoma. In most of the patients (61%), malignancy was the precipitating factor for CAPS. In 4 patients (17%), however, surgical procedures related to the carcinoma were noted as precipitating factors. In one patient CAPS occurred during allogenic stem cell transplantation after diagnosis of acute lymphoblastic leukemia (ALL). Cerebral manifestations were most common and consisted mainly of cerebral infarcts and encephalopathy. Recovery occurred in 9/23 (39%) patients. Malignancy may be an important risk factor for CAPS. 9% of patients with CAPS presented with an underlying malignancy. In most of these patients, the malignancy and/or surgical procedures were the precipitating factors for CAPS.

Keywords: Catastrophic antiphospholipid syndrome; Malignancy; Surgery; Thrombosis; Anticoagulation; Leukaemia

Contents

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The coincidence of malignancies and the presence of antiphospholipid antibodies (aPL) have been described in several important epidemiological studies [1–13]. The pathogenic role of aPL in patients with malignancies, however, is not clear. It has been repeatedly demonstrated that particularly haematological and lymphoproliferative malignancies may be associated with the generation of aPL, but do not necessarily enhance the thrombophilic risk in these patients.

A recent prospective epidemiological study on the occurrence of malignancies in aPL-positive patients [10] showed the presence of carcinoma in 14 of 72 aPL-positive patients. None of these patients, however, had a history of thrombosis. In one patient (with non-Hodgkin's lymphoma), however, the aPL disappeared when complete remission had been achieved.

This particularly serious and often fatal variant of the antiphospholipid syndrome (APS), although rare, is termed catastrophic APS (Asherson's Syndrome) [14] and has been reported as not uncommonly occurring in patients with underlying malignancies [15,16]. The syndrome is characterised by the rapid development of fulminant thrombotic complications that predominantly affect small vessels.

In this study, we evaluated the frequency and spectrum of malignancies in patients with CAPS in order to determine the influence of malignancies on CAPS.

We analysed the web site-based international registry of patients with catastrophic APS (the CAPS registry; http://www.med.ub.es/Mimmun/Forum/Caps.HTM). This registry was created by the European Forum on Antiphospholipid Antibodies in 2000 and is compiled of all published reports of patients with CAPS.

Up to February 2006, it included 262 patients: 187 female and 75 male.

The mean age (S.D.) was 38 (15) years (with a range of 7–76 years). 129 patients (49%) had primary APS, 102 patients suffered from systemic lupus erythematosus (SLE), 13 patients from lupus-like syndrome and 18 patients from other diseases (mainly rheumatoid arthritis and systemic sclerosis). Patients with a known history of malignancy were selected and analysed.

Of the 262 patients included in the CAPS registry, information on malignancy was available in 23 (9%) cases. Of these 14 (61%) were female and 9 (39%) male. The mean (S.D.) age was 46.9 (12) years (range: 32–71 years).

Six (26%) of the patients additionally had an underlying rheumatic disorder. Of these patients, three suffered from systemic lupus erythematosus (SLE), one from lupus-like disease, one from scleroderma and one from polymyositis.

Lupus anticoagulants were detected in 17 (74%) patients, IgG-anticardiolipin antibodies (aCL) in 15 (65%) and IgM-aCL in 7 (30%) patients. A low platelet count was found in 9 (39%) patients.

Haematological malignancies were present in 6 (26%) patients. These consisted of non-Hodgkin's lymphoma, acute lymphatic leukaemia, angiocentric lymphoma, chronic myelocytic leukaemia and Hodgkin's lymphoma. Four of the patients suffered from a lung carcinoma (17%) and two patients (9%) from a colon carcinoma.

The malignancy features are listed in Table 1.

In 12 (52%) patients, CAPS was the first manifestation of APS. In 11 (48%) patients with previously known APS, mostly cerebrovascular accidents, deep vein thromboses and fetal loss had previously occurred.

Cerebral manifestations were frequently found (65%) and consisted mainly of cerebral infarcts and encephalopathia.

Intra-abdominal involvement was identified in 13 (57%) patients, mainly consisting of splenic infarction, hepatic infarction, ileus, portal thrombi and Budd–Chiari syndrome.

Eleven patients (48%) suffered from deep vein thrombosis and one patient from ischemia of both extremities.

Pulmonary involvement was identified in 13 (57%) patients; mainly pulmonary embolism, acute respiratory distress syndrome (ARDS) and lung failure.

Nine patients (39%) had cardiac manifestations; mainly valve lesions, myocardial infarction, and heart failure.

Table 1
Malignancies in patients with CAPS

Patient number	Malignancies
1	Uterus carcinoma
2	Lung biopsy (adenocarcinoma)
3	Carcinoma
4	Gastric adenocarcinoma
5	Lung adenocarcinoma
6	Cholangiocarcinoma
7	Lymphoma
8	Abdominal surgery for reconstruction of colon; previous colectomy
9	Treatment of breast cancer
10	Adenocarcinoma of colon
11	Primary lung cancer
12	Epithelial carcinoma with unknown primary
13	Menigioma resection
14	Leiomyosarcoma, anticoagulation withdrawal
15	Carcinoid tumor, surgery
16	Lung adenocarcinoma
17	Non-Hodgkin lymphoma
18	Angiocentric lymphoma
19	Chronic myelomonocytic leukemia
20	Peripheral T-cell lymphoma
21	Ovarian cancer
22	Allogenic stem cell transplantation (acute lymphoblastic leukaemia)
23	Hodgkin's lymphoma

In 13 patients (56%) renal manifestations were found, mainly renal infarcts and renal failure.

Skin manifestations were reported in 10 patients (43%) and consisted of skin ulcers, livedo reticularis and gangrene.

Other manifestations were reported in single patients only. These consisted of thrombosis of the inferior cava vein and thrombotic microangiopathy, retinal vein occlusion and retina artery occlusion.

In most of the patients (61%), malignancy was noted as the precipitating factor for CAPS.

In 4 patients (17%), surgical procedures related to carcinoma were noted as precipitating factors; such as lung biopsy, mengioma resection, surgery for a carcinoid tumour or abdominal surgery for reconstruction of the colon after a previous colectomy.

Two patients presented with CAPS after anticoagulation withdrawal, one patient after treatment of breast cancer and one patient after allogenic stem cell transplantation (ALL).

In two patients, precipitating factors were not evident.

Most patients received a combination of treatments. Anticoagulation was used in 19 patients (83%), steroids in 14 (61%), plasma exchange in 9 patients (39%), cyclophosphamide in 7 (30%), haemodialysis in 4 (17%), aspirin in 3 (13%), prostacyclin in 3 patients (13%). One patient received intravenous gammaglobulin and one patient received thrombolysis.

Recovery occurred in 9/23 (39%) of catastrophic APS patients with malignancies.

Malignancy is an important factor precipitating the antiphospholipid syndrome, even though the pathogenic role of aPL is not clear in these patients.

In patients with CAPS, malignancy was observed in at least 9% of all cases. In 78% of these patients, malignancy or procedures associated with the malignancy were noted as precipitating factors. This emphasises the pathogenic role of malignancy in patients with CAPS.

Haematological and lymphoproliferative malignancies particularly may be associated with the generation of aPL, but their presence does not necessarily enhance the thrombophilic risk in these patients [8].

Haematological malignancies were present in 26% of CAPS patients and formed the largest identifiable group. Their presence, however, seems to be a strong risk factor for the development of CAPS.

The outlook for patients with the simultaneous occurrence of malignancies and CAPS is poor as only 39% of these patients recovered.

Although mechanisms leading to CAPS are still unclear, haemostatic changes caused by malignancies may contribute to the development of CAPS. Among the procoagulant mechanisms associated with malignancies, platelet activation [17], endothelial cell activation [18], and the expression of tissue factor [19] seem to be the most important factors, and these mechanisms have also been deemed relevant for the induction of APS itself.

In conclusion, malignancies may precede the development of catastrophic APS. Rapidly occurring and fulminant thrombotic complications seen in patients with malignancies should lead to the possible diagnosis of catastrophic APS, and patients may benefit from early and aggressive treatment of this often fatal syndrome.

Further studies are clearly required in order to investigate the specific circumstances under which CAPS might develop, and also to compare CAPS-patients with and without malignancies, in order to identify the risk factors pertinent to the development of this dramatic form of APS.

Take-home messages

- Malignancy may be an important risk factor for the catastrophic antiphospholipid syndrome.
- Nine percent of patients with CAPS presented with an underlying malignancy.
- In most of these patients, the malignancy and/or surgical procedures were the precipitating factors for CAPS.
- The prognosis is poor when the two conditions, malignancy and catastrophic antiphospholipid syndrome are combined.

Appendix A. The Catastrophic Antiphospholipid Syndrome Registry Project Group

The members of the Catastrophic APS Registry Project Group who contributed to this study are as follows: Christopher Davidson, Department of Cardiology, Royal Sussex Hospital, Brighton, UK; Alex E Denes, Division of Oncology, Department of Medicine, Washington University School of Medicine, St. Louis, USA; Ronald HWM Derksen, Department of Rheumatology and Clinical Immunology, University Medical Centre, Utrecht, The Netherlands; JF Diaz Coto, Caja Costarricense del Seguro Social, San Jose, Costa Rica; Patrick Disdier, Service de Medecine Interne, Centre Hospitalier Universitaire Timone, Marseille, France; Rita M Egan, Department of Medicine, University of Kentucky Medical Center, Lexington, USA; R Enriquez, Nephrology Section, Hospital General de Elche, Spain; Fernanfa Falcini, Department of Paediatrics, University of Florence, Italy; Leslie S Fang, Renal Associates, Massachusetts General Hospital and Harvard Medical School, Boston, USA; John T Grandone, Neenah, Wisconsin,

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References

[1] Asherson RA. Antiphospholipid antibodies, malignancies and paraproteinemias. J Autoimmun 2000;15:117–22.

[2] Bessis D, Sotto A, Viaid JP, Berard M, Civana AJ, Boffa M. Trousseau's syndrome with non-bacterial thrombotic endocarditis: pathogenetic role of antiphospholipid syndrome. Am J Med 1995;98:511–3.

[3] Faiderbe S, Chagnaud JL, Charrier MC, Peyron MA, Wafflart J, Geffard M, et al. Antibodies directed against lipid membrane components in sera of patients with malignant tumours. Cancer Detec Prev 1991;15:199–203.

[4] Genvresse I, Buttgereit F, Späth-Schwalbe E, Ziemer S, Eucker J, Possinger K. Arterial thrombosis associated with anticardiolipin and anti-β2-glycoprotein-I antibodies in patients with non-Hodgkin's lymphoma: a report of two cases. Eur J Haematol 2000;65:344–7.

[5] Liozon E, Loustaud V, Jauberteau MO, Jaccard A, Soria P, Bordessoule D, et al. Non-simultaneous malignant lymphoma and antiphospholipid syndrome: 4 cases. Rev Med Interne 2001;22:360–70.

[6] Lossos IS, Bogomolski-Yahalom V, Hatzner Y. Anticardiolipin antibodies in acute myeloid leukaemia: prevalence and clinical significance. Am J Hematol 1998;57:139–43.

[7] McNeil HP, Chesterman CN, Krilis SA. Immunology and clinical importance of antiphospholipid antibodies. Adv Immunol 1991;49:193–280.

[8] Miesbach W, Scharrer I, Asherson RA. Thrombotic manifestations of the antiphospholipid syndrome in patients with malignancies. Clin Rheumatol 2006;25:1–5.

[9] Piette J-C, Cervera R, Levy RA, Nasonov EL, Triplett DA, Shoenfeld Y. The Catastrophic Antiphospholipid Syndrome–Asherson's Syndrome. Ann Med Interne 2000;154:195–6.

[10] Schved JF, Dupuy-Fons C, Biron C, Quere I, Janbon C. A prospective epdimiological study of the occurrence of antiphospholipid antibody; the Montpelier Antiphospholipid (MAP) Study. Haemostasis 1994;24:175–82.

[11] Stasi R, Stipa E, Masi M, Oliva F, Sciarra A, Perrotti A, et al. Antiphospholipid antibodies: prevalence, clinical significance and correlation to cytokine levels in acute myeloid leukemia and non-Hodgkin's lymphoma. Thromb Haemost 1993;70:568–72.

[12] Yoon KH, Wong A, Shakespeare T, Sivalingham P. High prevalence of the antiphospholipid antibodies in Asian cancer patients with thrombosis. Lupus 2003;12:112–6.

[13] Zuckerman E, Toubi E, Golan T, Rosenvald-Zuckerman T, Sabo E, Shmuel Z, et al. Increased thromboembolic incidence in anticardiolipin-positive patients with malignancy. Br J Cancer 1995;72:447–51.

[14] Asherson RA, Cervera R, Piette JC, Shoenfeld Y, Espinosa G, Petri MA, et al. Catastrophic antiphospholipid syndrome. Clues to the pathogenesis from a series of 80 patients. Medicine (Baltimore) 2001;80:1–23.

[15] Yamamoto T, Ito M, Nagata S, Suzuki H, Togawa A, Nagase M, et al. Catastrophical exacerbation of antiphospholipid syndrome after lung adenocarcinoma biopsy. J Rheumatol 2000;27:2035–7.

[16] Soltesz P, Szekanecz Z, Vegh J, Lakos G, Toth L, Szakall S, et al. Catastrophic antiphospholipid syndrome in cancer. Haematologica 2000;30:303–11.

[17] Campbell AL, Pierangeli SS, Wellhausen S, Harris EN. Comparison of the effect of anticardiolipin antibodies from patients with the antiphospholipid syndrome and with syphilis on platelet activation and aggregation. Thromb Haemost 1995;73:529–34.

[18] Meroni PL, Raschi E, Camera M, Testoni C, Nicoletti F, Tincani A. Endothelial activation by aPL. A potential pathogenetic mechanism for the clinical manifestations of the syndrome. J Autoimmun 2000;15:237–40.

[19] Dobado-Berrios PM, Lopez-Pedreda C, Velazco F, Cuadrado MJ. The role of tissue factor in the antiphospholipid syndrome. Arthritis Rheum 2001;44:2467–76.

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ORIGINAL ARTICLE

The role of malignancies in patients with catastrophic anti-phospholipid (Asherson's) syndrome

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Abstract The catastrophic anti-phospholipid syndrome (CAPS) differs from the anti-phospholipid syndrome in its accelerated systemic involvement leading to multi-organic failure. In this study, the occurrence of malignancies in patients with CAPS was evaluated and the clinical findings of CAPS patients with and without malignancies were compared. We investigated the web site-based international registry of patients with CAPS for all cases in which both CAPS and underlying malignancies were present. The clinical characteristics of these cases were subsequently evaluated to establish common characteristics. The CAPS registry included information on a total of 262 cases. Twenty-three (9%) patients suffered from malignancies. In 78% of these patients, the malignancy itself or the treatment modalities instituted for the carcinoma was the precipitating factor of CAPS. Only 39% of CAPS patients with malignancies recovered in comparison to 58% of patients without malignancies ($p=0.07$). Treatment modalities, however, did not differ significantly between these patients. Infections were not evident as precipitating factors for any of the malignancy patients. The mean age of patients with malignancies was 9 years older than the average age of other patients with CAPS and the prevalence of SLE was significantly less common than in patients without malignancy. Malignancy may play a pathogenic role in patients with CAPS, whereas infections are more important as triggering factors in patients without malignancies. CAPS patients with malignancies are generally older than CAPS patients without malignancies; they generally have the worst prognosis of the entire CAPS cohort.

Keywords Anti-phospholipid syndrome · Carcinoma · Catastrophic · Malignancy · Thrombosis

*The members of the Catastrophic Antiphospholipid Syndrome Registry Project Group are listed in the Appendix.

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Introduction

A particularly serious clinical form of the anti-phospholipid syndrome with a mortality rate of approximately 50%, despite treatment, has been termed the catastrophic anti-phospholipid syndrome (Asherson's syndrome or CAPS). [1–5]. In the majority of cases, these patients present with fulminant thrombotic complications predominantly affecting small vessels of organs particularly. Large vessel occlusions *do* occur but with a considerably reduced frequency to their occurrence in the simple/classic anti-phospholipid syndrome (APS). These consist of deep vein thromboses, complicated by pulmonary embolism or major arterial occlusions, e.g. stroke most frequently.

Despite our increasing understanding of the underlying mechanisms and clinical manifestations of CAPS, thrombotic complications are nevertheless still unpredictable and "triggering factors" are not identifiable in the majority of cases. Risk factors are increasingly being identified. These include warfarin withdrawal, surgery or prior infections. One important risk factor for CAPS appears to be a history of malignancy [6, 7].

The coincidence of malignancies and the presence of anti-phospholipid antibodies (aPL) has been described in several important epidemiological published studies [8–13]. It has been repeatedly demonstrated that particular haematological and lymphoproliferative malignancies may be associated with the development of aPL, but their presence may not necessarily enhance the thrombophilic risk in these patients. This has been highlighted in a recent paper by Miesbach et al., showing that even high levels of the IgM isotype does not appear to be associated with any thrombophilic risk [14].

A prospective epidemiological study on the occurrence of malignancies in aPL-positive patients showed the presence of carcinoma in 14 of 72 aPL-positive patients. None of these patients, however, had a history of thrombosis and in one patient with non-Hodgkin's lymphoma, aPL disappeared when complete remission had been achieved [15].

In this study, the occurrence of malignancies in patients with CAPS was evaluated, the clinical findings of CAPS and the outcome of patients with and without malignancies were compared.

Materials and methods

We analysed all cases included in the CAPS registry, a web site-based international registry of patients with CAPS (http://www.med.ub.es/Mimmun/Forum/Caps.HTM). This registry was created by the European Forum on Antiphospholipid Antibodies in 2000 and is a compilation of all published reports of patients with CAPS.

In February 2006, the CAPS registry included 262 patients: 187 (71%) female and 75 (29%) male. The mean age of the patients at the occurrence of CAPS was 38 years (range 7 to 76 years) [15]. One hundred twenty-nine (49%) patients had primary APS, 102 patients suffered from systemic lupus erythematosus (SLE), 13 patients from lupus-like syndrome and 18 patients from other diseases (mainly rheumatoid arthritis and systemic sclerosis). We selected patients with a history of malignancies and compared the clinical features to those without any history of malignancies. In cases of malignancy, diagnosis was confirmed by biopsy or post-mortem autopsy. Fisher's exact test (bilateral) was used for all statistical tests.

Results

General characteristics and APS-related laboratory findings

Of the 262 cases included in the CAPS registry, 23 (9%) suffered from malignancies. Of these cases, 14 (61%) were female and 9 (39%) were male. The mean age was 46.9 years with a standard deviation of 12 years (range 32 to 71 years). Of the patients, 6 (26%) had an underlying rheumatic disorder. Of these patients, three suffered from systemic lupus erythematosus (SLE), one from lupus-like disease, one from scleroderma and one from poly-myositis. Lupus anti-coagulants were detected in 17 (74%) patients, IgG–aCL in 15 (65%) patients and IgM–aCL in 7 (30%) patients. Thrombocytopenia was present in 9 (39%) patients.

Malignancy features

Haematological malignancies were present in 6 (26%) patients: lymphoma, non-Hodgkin's lymphoma, acute lymphatic leukaemia, angiocentric lymphoma, chronic myelocytic leukaemia and Hodgkin's lymphoma. The other patients suffered mainly from lung carcinoma (17%). Two (9%) patients had colon carcinoma. The features of the malignancies are listed in Table 1.

Clinical presentations and precipitating factors

Cerebral manifestations were frequently found (65%), mainly cerebral infarcts and encephalopathy.

Intra-abdominal involvement was identified in 13 (57%) patients; mainly splenic and hepatic infarctions, portal thrombi and Budd–Chiari syndrome and ileus (mostly due to bowel infarctions).

Eleven (48%) patients suffered from deep vein thrombosis and 1 patient suffered from ischaemia of both extremities.

Pulmonary involvement was identified in 13 (57%) patients. The main manifestations were pulmonary embolism, acute respiratory distress syndrome (ARDS) and lung failure.

Nine (39%) patients had cardiac manifestations; mainly valve lesions, myocardial infarction and heart failure.

In 13 (56%) patients, renal manifestations were evident; mainly renal failure (9 patients) and renal infarcts (6 patients).

Skin manifestations were reported in 10 patients (43%) and consisted of skin ulcers, livedo reticularis and gangrene.

The following manifestations were reported in one patient each: thrombosis of the inferior cava vein, thrombotic micro-angiopathy, retinal vein occlusion and retinal artery occlusion.

Table 1 Malignancy features of patients with CAPS

Case	Sex	Age	Malignancy features
1 (68)	F	33	Uterus carcinoma
2 (86)	M	60	Lung biopsy adenocarcinoma
3 (88)	M	41	Carcinoma
4 (96)	F	45	Gastric adenocarcinoma
5 (98)	F	40	Lung adenocarcinoma
6 (118)	M	38	Cholangiocarcinoma
7 (122)	F	69	Lymphoma
8 (128)	F	32	Abdominal surgery for reconstruction of colon; previous colectomy
9 (156)	F	43	Treatment for breast cancer
10 (157)	F	61	Adenocarcinoma in colon
11 (168)	M	50	Primary lung cancer
12 (186)	M	52	Epithelial carcinoma with unknown primary
13 (206)	F	35	Menigioma resection
14 (208)	F	52	Leiomyosarcoma, anti-coagulation withdrawal
15 (215)	F	32	Carcinoid tumour, surgery
16 (216)	M	48	Lung adenocarcinoma
17 (217)	M	36	Non-Hodgkin lymphoma
18 (218)	F	41	Angiocentric lymphoma
19 (219)	M	71	Chronic myelomonocytic leukaemia
20 (220)	M	65	Peripheral T cell lymphoma
21 (252)	F	44	Ovarian cancer
22 (254)	F	44	Allogenic stem cell transplantation (acute lymphoblastic leukaemia)
23 (255)	F	NR	Hodgkin's lymphoma

The numbers in the parentheses correspond to the number of the case in the CAPS registry.

In most of the patients (61%), the malignancy was recorded as the precipitating factor for CAPS.

In 4 (17%) patients, surgical procedures related to the treatment of the carcinoma were listed as being the precipitating factor. These procedures included lung biopsy, meningioma resection, carcinoid and abdominal surgery for reconstruction of the colon after a previous colectomy.

Two patients presented with CAPS after anti-coagulation withdrawal, one patient after treatment for breast cancer and one patient after allogenic stem cell transplantation (ALL).

In two patients, the precipitating factors were not recorded.

The first manifestation of APS in patients with malignancies was mostly neurological.

The period for the development of CAPS was less than a week in six patients and more than a week in three patients. The time frame was not recorded in the other patients.

Treatment and outcome

Most patients received a combination of treatments. Anti-coagulation was used in 19 (83%) patients, steroids in 14 (61%), plasma exchange in 9 (39%), cyclophosphamide in 7 (30%), haemodialysis in 4 (17%), aspirin in 3 (13%) and prostacyclin in 3 (13%). One patient received intravenous gamma globulin and one patient received thrombolysis.

Recovery from CAPS occurred in 9/23 (39%) cases. The patients received the following treatment modalities: 9/19 (47%) of those treated with anti-coagulation recovered vs none of the 4 patients not given this treatment. Of those treated with steroids, 3/13 (23%) recovered vs 6/9 (67%) of those not given steroids. Of those treated with plasma exchange, 3/9 (33%) recovered vs 6/14 (43%) without this treatment. Of those treated with cyclophosphamide, 2/7 (28%) recovered vs 7/15 (47%) of cases who did not receive this treatment.

Comparison of CAPS patients with and without malignancies

The profiles of the demographic characteristics (except for the age of the patients), immunological findings and clinical features were similar. The mean age of the patients with malignancies was higher at 47 years with a SD of 12 years (range 32 to 71 years) than in patients without malignancies who had a mean age of 38 years and a SD of 15 years (range 7 to 76 years).

Of the patients with malignancy, 6 (26%) had an underlying rheumatic disorder. One hundred twenty-six (53%) patients without malignancies had an underlying rheumatic disorder. This was mostly SLE (87%). The prevalence of SLE was significantly higher than in patients with malignancies ($p<0.05$).

CAPS was the first manifestation of APS in 12 (52%) patients. In 11 (48%) patients in whom the presence of APS was already known, the most common prior manifestations were mostly cerebrovascular accidents, deep vein thromboses and fetal loss. CAPS was also the first manifestation in 45% of the patients without malignancies (p=0.3).

In most patients (78%), malignancies themselves or procedures associated with the malignancy were recorded as the precipitating factors. In patients without malignancies, however, infections were the most frequent precipitating factors in 52/239 (22%) cases. The precipitating conditions most commonly reported were not found to apply in the patients with malignancies, e.g. the prevalence of infection as a precipitating factor differed entirely between patients with and without malignancies (22% vs 0%, p<0.005).

Only 9/23 (39%) of CAPS patients with malignancies recovered, whereas 138/239 (58%) of those without malignancies (p=0.07) did so. Treatment modalities, however, did not differ significantly between patients with and without malignancies. Anti-coagulation was given in 83% of cases with malignancies and in 81% of those without malignancies; steroids in 74% vs 61%; cyclophosphamide in 30% vs 30%; immunoglobins in 4% vs 22%; and aspirin in 13% vs 8%.

Treatment with plasma exchange, however, was noted more frequently in patients with malignancies: 39% vs 29% (p=0.2). Haemodialysis was used in 17% of patients with and without malignancies.

Discussion

The catastrophic anti-phospholipid syndrome is a rare sub-set of the anti-phospholipid syndrome that differs from anti-phospholipid syndrome by its accelerated systemic involvement leading to multi-organic failure. In patients with APS, it is well-known that a wide variety of infections may be associated with thrombotic events [16].

Recently, "triggering factors" for CAPS were identified in 51% of the patients [17]. Most importantly, common infections (bacterial or viral) were identified in 24% of the patients. Severe infections, such as refractory infections occurring in leg ulcers also occurred [18]. The other factors preceding CAPS were anti-coagulation withdrawal, trauma and malignancies.

In the current study, malignancies were identified in 9% of patients with CAPS. Without any control group it cannot be concluded that the frequency of malignancies differs from any other APS patient population. However, it seems that malignancies might occur in CAPS patients more frequently than expected, although there is no hard data available to support this.

In 78% of the patients of our study, *the malignancies themselves or procedures* associated with the treatment of a malignancy were identified as precipitating factors of CAPS. This suggests the pathogenic role of malignancy in patients with CAPS. Infections were not recorded for any of the patients with malignancy, which is significantly different to patients without malignancies. It should be noted, however, that due to the rare occurrence of CAPS, the small CAPS patient population with malignancies might stress the statistical meaningfulness of this study.

Another significant difference is that the mean age of patients with malignancies was 9 years higher than in patients without malignancies. It is well-known that the prevalence of malignancies is higher in the elderly but it can also be hypothesised that in cases with underlying malignancies, CAPS may affect patients of an older age group.

Underlying rheumatic diseases such as SLE do not seem to play the same major role that they do in patients without malignancies. The prevalence of SLE was significantly lower in patients with malignancies than in patients without malignancies.

Prior APS manifestations were present in nearly one half of the patients. A few reports describe patients in whom a diagnosis of a "primary" anti-phospholipid syndrome had evolved into a malignant disease after several years [19].

The form and diversity of clinical manifestations did not differ between patients with or without malignancies. It has been reported, however, that some distinct APS manifestation, such as livedo reticularis, seem to occur more often in CAPS patients than in APS patients [20].

Haematological and lymphoproliferative malignancies particularly may be associated with the development of aPL, but their presence does not necessarily enhance the thrombophilic risk in these patients [20–22]. However, it seems evident that aPL may contribute to the occurrence of thrombosis in the condition previously referred to as Trousseau's syndrome [24].

It was striking that haematological malignancies were present in 26% of CAPS patients and formed the largest single group of malignancies.

Limited by the nature of the CAPS registry, no detailed information about the type of therapy (e.g. immunosuppressives) of patients with malignancy was available.

The survival rate of patients with CAPS is poor and the optimal treatment for patients with CAPS has not yet been established. The outcome of patients with CAPS is worse in the presence of an additional malignancy than when no malignancy is present. Only 39% of CAPS patients with malignancies recovered. This may be due to the additional presence of the malignancy and to the older age of the patients. Other confounding factors were not found. Treatment modalities did not differ significantly between

patients with and without malignancies. Treatment by plasma exchange, however, was used more frequently in patients with malignancies. The poorer survival rate in patients with malignancies might have nothing to do with the treatment modalities.

It has recently been demonstrated that most survivors of CAPS did not develop any further thrombotic events [23]. An important publication by Bucciarrelli et al. [26] has also shown that the prognosis for CAPS seems to have improved from 2001 to 2006 and this may be dependent on the treatment guidelines established for this condition.

It is worthy to note that no further CAPS episodes occurred, particularly in the surviving patient group with malignancies.

Conclusions

Malignancy may play a pathogenic role in patients with CAPS, whereas infections are more important as being a triggering factor in patients without malignancies. Of the patients with CAPS, 9% presented with an underlying malignancy. In most of these patients, either the malignancy itself or surgical procedures related to the malignancy were the precipitating factors for CAPS. CAPS patients with malignancies are generally older than CAPS patients without malignancies. They generally have the worst prognosis of the entire CAPS cohort.

Thus, rapidly occurring and fulminant thrombotic complications in patients with malignancies should lead clinicians to consider the diagnosis of CAPS. These patients may benefit from the early treatment of this syndrome.

Appendix

The Catastrophic Antiphospholipid Syndrome Registry Project Group

The members of the Catastrophic APS Registry Project Group who contributed to this study are as follows: Christopher Davidson, Department of Cardiology, Royal Sussex Hospital, Brighton, UK; Alex E Denes, Division of Oncology, Department of Medicine, Washington University School of Medicine, St Louis, USA; Ronald H W M Derksen, Department of Rheumatology and Clinical Immunology, University Medical Centre, Utrecht, The Netherlands; J F Diaz Coto, Caja Costarricense del Seguro Social, San Jose, Costa Rica; Patrick Disdier, Service de Medecine Interne, Centre Hospitalier Universitaire Timone, Marseille, France; Rita M Egan, Department of Medicine, University of Kentucky Medical Center, Lexington, USA; R Enriquez, Nephrology Section, Hospital General de Elche, Spain; Fernanfa Falcini, Department of Paediatrics, University of Florence, Italy; Leslie S Fang, Renal Associates, Massachusetts General Hospital and Harvard Medical School, Boston, USA; John T Grandone, Neenah, Wisconsin, USA; Anagha Gurjal, Division of Hematology/Oncology, Barbara Ann Karmanos Cancer Institute, Detroit, Michigan, USA; Gilles Hayem, Department of Rheumatology, CHU Bichat-Claude-Bernard, Paris, France; Graham R V Hughes, Lupus Research Unit, The Rayne Institute, St Thomas' Hospital, London, UK; Sohail Inam, Riyadh Armed Forces Hospital Riyadh, Saudi Arabia; K Shashi Kant, Department of Internal Medicine, University of Cincinnati College of Medicine, Ohio, USA; Craig S Kitchens, Department of Medicine, University of Florida, Gainesville, USA; Michael J Kupferminc, Department of Obstetrics and Gynaecology, Lis Maternity Hospital, Tel Aviv University, Tel Aviv, Israel; Roger A Levy, Department of Rheumatology, Faculdade de Ciencias Medicas, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil; Siu Fai Lui, Department of Medicine, Prince of Wales Hospital and Chinese University of Hong Kong, Shatin, Hong Kong; Peter J Maddison, Gwynedd Rheumatology Service, Ysbyty Gwynedd, Bangor, UK; Yoseph A Mekori, Department of Medicine, Meir Hospital, Kfar Saba, Israel; Takako Miyamae, Department of Paediatrics, Yokohama City University School of Medicine, Yokohama, Japan; John Moore, Department of Haematology, St Vincent's Hospital, Sydney, Australia; Francisco J Munoz-Rodriguez, Department of Autoimmune Diseases, Hospital Clinic, Barcelona, Catalonia, Spain; Ayako Nakajima, Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan; Michael C Neuwelt, Medical Service, VA Palo Alto Health Care System, USA; Ann Parke, Department of Internal Medicine, Division of Rheumatic Diseases, University of Connecticut Health Center, Connecticut, USA; Jorge Rojas-Rodriguez, Department of Rheumatology, Specialties Hospital, Manuel Avila Camacho National Medical Centre, Puebla, Mexico; Allen D Sawitzke, Division of Rheumatology, Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City, USA; Cees G Schaar, Department of Haematology, Leiden University Medical Centre, The Netherlands; Yehuda Shoenfeld, Chaim-Sheba Medical Centre, Tel-Hashomer, Israel; Alex C Spyropoulos, Clinical Thrombosis Center, Albuquerque, New Mexico, USA; Carlos Vasconcelos, Hospital Geral de San Antonio, Poro, Portugal; and Margaret Wislowska, Outpatients Department of Rheumatology, Central Clinical Hospital,Warsaw, Poland.

References

1. Piette JC, Cervera R, Levy RA, Nasonov EL, Triplett DA, Shoenfeld Y (2000) The catastrophic antiphospholipid syndrome—Asherson's syndrome. Ann Med Interne (Paris) 154(4):195–196

2. Asherson RA (1992) The catastrophic antiphospholipid syndrome. J Rheumatol 19(4):508–512
3. Triplett DA, Asherson RA (2000) Pathophysiology of the catastrophic antiphospholipid syndrome (CAPS). Am J Hematol 65(2):154–159
4. Asherson RA, Cervera R, de Groot PG, Erkan D, Boffa MC, Piett JC et al (2003) Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines. Lupus 12(7):530–534
5. Cervera R, Font J, Gómez-Puerta JA, Espinosa G, Cucho M, Bucciarelli S, Ramos-Casals M, Ingelmo M, Piette JC, Shoenfeld Y, Asherson RA, Catastrophic Antiphospholipid Syndrome Registry Project Group (2005) Validation of the preliminary criteria for the classification of catastrophic antiphospholipid syndrome. Ann Rheum Dis 64(8):1205–1209
6. Asherson RA (2000) Antiphospholipid antibodies, malignancies and paraproteinemias. J Autoimmun 15(2):117–122
7. Asherson RA, Cervera R, Piette JC et al (2001) Catastrophic antiphospholipid syndrome: clues to the pathogenesis from a series of 80 patients. Medicine (Baltimore) 80:1–23
8. Soltesz P, Szekanecz Z, Vegh J, Lakos G, Toth L, Szakall S, Veres K, Szegedi G (2000) Catastrophic antiphospholipid syndrome in cancer. Haematologica 30(4):303–311
9. Lossos IS, Bogomolski-Yahalom V, Hatzner Y (1998) Anticardiolipin antibodies in acute myeloid leukemia: prevalence and clinical significance. Am J Hematol 57(2):139–143
10. Stasi R, Stipa E, Masi M, Oliva F, Sciarra A, Perrotti A, Zaccari G, Papa G (1993) Antiphospholipid antibodies: prevalence, clinical significance and correlation to cytokine levels in acute myeloid leukemia and non-Hodgkin's lymphoma. Thromb Haemost 70(4):568–572
11. Miesbach W, Scharrer I, Asherson RA (2006) Thrombotic manifestations of the antiphospholipid syndrome in patients with malignancies. Clin Rheumatol 25(6):840–844
12. Yoon KH, Wong A, Shakespeare T, Sivalingam P (2003) High prevalence of the antiphospholipid antibodies In Asian cancer patients with thrombosis. Lupus 12(2):112–116
13. Zuckerman E, Toubi E, Golan TD et al (1995) Increased thromboembolic incidence in anticardiolipin-positive patients with malignancy. Br J Cancer 72(2):447–451
14. Miesbach W, Scharrer I, Asherson RA (2007) High titres of IgM-antiphospholipid antibodies are unrelated to pathogenicity in patients with non-Hodgkin's lymphoma. Clin Rheumatol 26 (1):95–97
15. Schved JF, Dupuy-Fons C, Biron C et al (1994) A prospective epdimiological study of the occurrence of antiphospholipid antibody: the Montpellier Antiphospholipid (MAP) Study. Haemostasis 24(3):175–182
16. Cervera R, Asherson RA, Acevedo ML, Gómez-Puerta JA, Espinosa G, De La Red G, Gil V, Ramos-Casals M, Garcia-Carrasco M, Ingelmo M, Fontr J (2004) Antiphospholipid syndrome associated with infections: clinical and microbiological characteristics of 100 patients. Ann Rheum Dis 63(10):1312–1317
17. Cervera R, Gómez-Puerta JA, Espinosa G, Font J, De La Red G, Gil V, Bucciarelli S et al (2003) "CAPS registry". A review of 200 cases from the international registry of patients with catastrophic antiphospholipid syndrome (CAPS). Ann Rheum Dis 62(Suppl 1):88
18. Amital H, Levy Y, Davidson C, Lundberg I, Harju A, Kosach Y, Asherson RA, Shoenfeld Y (2001) Catastrophic antiphospholipid syndrome: remission following leg amputation in 2 cases. Semin Arthritis Rheum 31(2):127–132
19. Asherson RA, Davidge-Pitts MC, Wypkema E (2006) "Primary" antiphospholipid syndrome evolving into Waldenstrom's macroglobulinaemia: a case report. Clin Rheumatol 26(2):278–280
20. Asherson RA, Frances C, Iaccarino L, Khamashta MA, Malacarne F, Piette JC, Tincani A, Doria A (2006) The antiphospholipid antibody syndrome: diagnosis, skin. Clin Exp Rheumatol 24(1 Suppl 40):S46–S51
21. Pusterla S, Previtali S, Marziali S et al (2004) Antiphospholipid antibodies in lymphoma: prevalence and clinical significance. Hematol J 5(4):341–346
22. Genvresse I, Lüftner D, Späth-Schwalbe E, Buttgereit F (2002) Prevalence and clinical significance of anticardiolipin and anti-β2-glycoprotein-I antibodies in patients with non-Hodgkin's lymphoma. Eur J Haematol 68(2):84–90
23. Timuragaoglu A, Duman A, Ongut G, Saka O, Karadogan I (2000) The significance of autoantibodies in non-Hodgkin's lymphoma. Leuk Lymphoma 40(1):119–122
24. Trousseau A (1865) Phlegmasia alba dolens. In: Clinique Medical de L'Hotel Dieu de Paris, vol 3. New Sydenham Society, London, 94 p
25. Erkan D, Asherson RA, Espinosa G, Cervera R, Font J, Piette JC et al (2003) Long term outcome of catastrophic antiphospholipid survivors. Ann Rheum Dis 62(6):530–533
26. Bucciarelli S, Espinosa F, Cervera R, Erkan D, Ramos-Casals M, Lockshin MD, Font J, Asherson RA (2007) Mortality in the catastrophic antiphospholipid syndrome: prognostic factors in a series of 250 patients. Arthritis Rheum (in press)

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Antiphospholipid syndrome in Latin American patients: clinical and immunologic characteristics and comparison with European patients

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The objective of this study was to analyse the prevalence and characteristics of the main clinical and immunological manifestations at the onset and during the evolution of the disease in a cohort of patients from Latin America (mainly of mestizo origin) and to compare the Latin American with the European patients. Clinical and serological characteristics of 100 APS patients from Mexico and Ecuador were collected in a protocol form that was identical to that used to study the 'Euro-Phospholipid' cohort. The cohort consisted of 93 female patients (93.0%) and seven (7.0%) male patients. There were 91 mestizos (91.0%), seven whites (7.0%) and two Amerindians (2.0%). The most common manifestations were *livedo reticularis* (40.0%), migraine (35.0%), inferior extremity deep vein thrombosis (32.0%), thrombocytopenia (28.0%) and hemolytic anemia (20.0%). Several clinical manifestations were more prevalent in Latin American than in European patients and they included mainly neurological (migraine, transient global amnesia, acute ischemic encephalopathy, amaurosis fugax) and cutaneous (*livedo reticularis*, skin ulcerations, superficial cutaneous necrosis, multiple subungual splinter hemorrhages) manifestations as well as hemolytic anemia. The APS has a wide variety of clinical and immunological manifestations at the onset and during the evolution of the disease and the ethnic origin in addition to environmental and socioeconomic factors can modify the disease expression. *Lupus* (2007) **16**, 366–373.

Key words: anticardiolipin antibodies; antiphospholipid antibodies; antiphospholipid syndrome; ethnicity; lupus anticoagulant

Introduction

The antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterized by a combination of arterial and/or venous thrombosis, recurrent fetal losses, often accompanied by a mild-to-moderate thrombocytopenia, and elevated titres of antiphospholipid antibodies (aPL), namely the lupus anticoagulant (LA) and/or the anticardiolipin antibodies (aCL).[1] First recognized in patients with systemic lupus erythematosus (SLE) and later less frequently in other autoimmune disorders, it is now well known that the development of this syndrome may also be independent of any underlying disease, being termed 'primary' APS.[2] More recently, another subset has been described in which multiple vascular occlusive events, usually affecting small vessels supplying organs and presenting over a short period of time, are the outstanding features. This subset has been termed 'catastrophic' APS.[3]

A great variety of clinical and immunological features have been described in patients with the APS.[4–7] Furthermore, the association with SLE, the gender, or the age at onset of the disease modify the disease

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expression and define some specific APS subsets, according to the larger epidemiological study performed in a European (mainly white) cohort ('Euro-Phospholipid' cohort).[8] However, a question that arises is whether the genetic background due to the ethnic origin can also modify the disease expression. Several investigators have addressed this problem with mixed results,[9,10] probably due to the small number of patients that have been analysed, the disparity in selection criteria for patient inclusion, and the definition of the variables.

The aims of this study were to analyse the prevalence and characteristics of the main clinical and immunological manifestations at the onset and during the evolution of the disease, in a cohort of 100 APS patients from Latin America (mainly of mestizo origin) using a standardized data-base protocol identical to that used to study the 'Euro-Phospholipid' cohort,[8] and to compare the mestizo Latin American with the white European patients in order to assess if the ethnic origin can modify the disease expression in the APS.

Methods

Patient selection

The cohort included 100 consecutive and unselected patients from two geographical areas of Latin America (Mexico and Ecuador) who met the criteria for the classification of definite APS.[11] Equivocal cases or those who did not fulfill these criteria were not included in this cohort.

The patients had been attending the Departments of Rheumatology at Hospital General Regional #36 and Hospital Guadalupe, Puebla, Mexico, and the Unidad de Enfermedades Reumáticas y Autoinmunes (UNERA), Hospital Monte Sinaí, Cuenca, Ecuador, either as in- or out-patients between the years 2000 and 2005. Staff of these two centres had substantial experience in the management of patients with APS. All the patients had medical histories documented and underwent medical interview as well as routine general physical examination by a qualified internist and/or rheumatologist. A serum sample from each patient was collected for the immunological tests. Clinical and serological characteristics of all these patients were prospectively collected in a protocol form that was identical to that used to study the 'Euro-Phospholipid' cohort and that has been fully described elsewhere.[8] Salient features included in this protocol were: 1) gender, 2) race, 3) age at onset of the disease, defined as the initial manifestation attributable to APS, 4) age at protocol, defined as the age when the patient entered in the protocol study, 5) underlying autoimmune disease, 6) clinical manifestations at the onset, 7) cumulative clinical manifestations during the evolution of the disease (from the onset until the protocol study), and 8) laboratory features at protocol. Information collected into the protocol forms was transferred to a computerized data-base program (Access 2.0). The study was performed according to the principles of the Declaration of Helsinki.

Definition of clinical features

In order to minimize possible inter-observer bias, the inclusion criteria and the variables of this protocol were carefully discussed by all the participating physicians on several occasions. Ethnic group was defined as white (individuals with all white European ancestors), amerindian (individuals with all Amerindian ancestors) and mestizo (individuals born in Latin America who had both Amerindian and white ancestors).[9] The underlying autoimmune disease was considered when the following criteria were present: 1) SLE: classified according to the American College of Rheumatology (ACR) revised criteria;[12] 2) lupus-like syndrome: if they fulfilled only two to three ACR criteria for SLE; 3) rheumatoid arthritis: classified according to the ACR criteria;[13] 4) dermatomyositis: classified according to Bohan and Peter's criteria;[14] 4) systemic sclerosis: classified according to the ACR preliminary criteria;[15] 6) primary Sjögren's syndrome: classified according to the European criteria;[16] 7) systemic vasculitis: classified according to the ACR criteria;[17] 8) primary APS: if they did not fulfill classification criteria for any of the previous conditions.

A total of 102 clinical manifestations that have been described in patients with APS[18] were included in the protocol forms. Patients were considered as having these manifestations if the diagnosis was firmly confirmed according to the established criteria for each manifestation using laboratory, imaging or doppler studies or histopathology, with the exception of superficial venous thrombosis and other dermatologic features that could be diagnosed on clinical grounds. For histopathologic confirmation of thrombosis, no significant evidence of inflammation should be present in the vessel wall. Specifically, among the major clinical manifestations, deep vein thrombosis was confirmed by doppler studies and/or phlebography, peripheral arterial thrombosis by arteriography, cerebro-vascular accident, multiinfarct dementia, acute ischemic encephalopathy, cerebral venous thrombosis and transverse myelopathy by computed tomography (CT) and/or magnetic resonance imaging (MRI) scans, migraine was diagnosed if the patient fulfilled the criteria of the International Headache Society,[19] pulmonary embolism was confirmed by ventilation/perfusion pulmonary

scintigraphy, heart valve lesions by transthoracic echocardiogram, myocardial infarction by elevated cardiac enzymes and electrocardiogram, and intraabdominal infarctions by CT and/or MRI scans. Patients were considered as having catastrophic APS if they presented with an acutely devastating APS with multiple organ involvement, as previously defined.[3] Pregnancy morbidity was considered when fulfilled the definitions established at the updated criteria for the classification of the APS.[11]

Laboratory studies

The aCL of the IgG and IgM isotypes were measured by a β_2-glycoprotein I (β_2GPI) dependent enzyme-linked immunosorbent assay (ELISA).[20] They were considered positive if present in medium to high titer ($>$15 GPL or $>$6 MPL) on two or more occasions, at least eight weeks apart. LA activity was detected by coagulation assays following the guidelines of the International Society on Thrombosis and Hemostasis (Scientific Subcommittee on Lupus Anticoagulants/Phospholipid-Dependent Antibodies),[21] in the following steps: 1) prolonged phospholipid-dependent coagulation demonstrated on a screening test, eg, activated partial thromboplastin time, kaolin clotting time, dilute Russell's viper venom time, dilute prothrombin time, Textarin time; 2) failure to correct the prolonged coagulation time on the screening test by mixing with normal platelet-poor plasma; 3) shortening or correction of the prolonged coagulation time on the screening test by the addition of excess phospholipid; 4) exclusion of other coagulopathies, ie, factor VIII inhibitor or heparin, as appropriate.

Antinuclear antibodies (ANA) were determined by indirect immunofluorescence using mouse liver and Hep-2 cells as substrate. Anti-dsDNA antibodies were determined with Farr's ammonium sulfate precipitation technique, ELISA and indirect immunofluorescence with Crithidia luciliae as substrate. Precipitating antibodies to extractable nuclear antigens (ENA), including Ro(SSA), La(SSB), U1-snRNP and Sm were detected by ELISA and counterimmunoelectrophoresis using calf and rabbit thymus and human spleen extracts. Rheumatoid factor (RF) was detected by latex and Waaler-Rose tests. All these tests were performed in referral laboratories that adhere to strict quality controls and that are participating in the standardization project of the European Forum on aPL.

Statistical analysis

Conventional chi-square and Fisher's exact tests were used for analysing qualitative differences, and Student's *t*-test for comparison of means in large independent samples of similar variance. A $P < 0.05$ was taken to indicate statistical significance. When several independent variables appeared to have statistical significance in the univariate analysis, a logistic regression test was performed for multivariate analysis in order to rule out possible confounding variables. In this case, only those variables showing statistical significance in the multivariate analysis were considered as significant in the results of the study. The odds ratio (OR) was calculated for assessing the risk of appearance of each variable. A lower limit of the 95% confidence interval (CI) that exceeded 1.0 was taken to indicate statistical significance in the case of positive association and an upper limit lower than 1.0 in the case of negative association. Results of the analysis of continuous variables are indicated as mean $\pm$ standard deviation (SD). This statistical analysis was performed by means of the SPSS program using the information stored in the data-base program.

Results

General characteristics

The cohort consisted of 100 patients (the half belonging to each centre with comparable clinical and immunologic characteristics). Ninety-three (93.0%) patients were female and there were 91 mestizos (91.0%), seven whites (7.0%) and two Amerindians (2.0%). The mean $\pm$ SD age at the onset of symptoms attributable to the disease was 28.2 $\pm$ 10.8 years (range, 8–65 years; median, 27). The mean $\pm$ SD age at study entry was 34.4 $\pm$ 11.8 years (range, 9–80 years; median, 34). The mean $\pm$ SD period of evolution of the disease until entry into the study had been 77 $\pm$ 54.4 months (range, 6–240 months; median, 70). Fifty-seven percent of patients were diagnosed as having primary APS, 35.0% had APS associated with SLE, 3.0% had APS associated with lupus-like syndrome, and 5.0% associated with others diseases. A catastrophic APS was not diagnosed in any patient. The comparison of the genders, ages, periods of evolution of the disease and underlying conditions between this Latin American cohort and the 'Euro-Phospholipid' cohort showed no statistical differences.

Clinical manifestations

The most common presenting manifestations in this cohort were *livedo reticularis* (32.0%), deep vein thrombosis (31.0%), thrombocytopenia (27.0%), migraine (25.0%), haemolytic anemia (19.0%), skin ulcerations (14.0%), amaurosis fugax (11.0%), stroke (10.0%), superficial cutaneous necrosis (10.0%), valve

thickening/dysfunction (9.0%), multiple subungueal splinter hemorrhage (9.0%) and inferior extremity superficial thrombophlebitis (8.0%) (Table 1).

A great variety of clinical manifestations were recorded during the evolution of the disease in vessels from almost any organ systems. The most common cumulated manifestations from disease onset until the protocol study were *livedo reticularis* (40.0%), migraine (35.0%), inferior extremity deep vein thrombosis (32.0%), thrombocytopenia (28.0%), haemolytic anaemia (20.02%), amaurosis fugax (11.0%), stroke (10.0%), superficial cutaneous necrosis (10.0%), valve thickening/dysfunction (9.0%) and subungueal splinter hemorrhages (9.0%) (Table 1).

Table 1 Clinical manifestations at disease onset and during the evolution of the disease of 100 Latin American patients with APS

Manifestations	*At disease onset No. (%)*	*Cumulated during the evolution of the disease No. (%)*
Peripheral thrombosis		
Inferior extremity deep vein thrombosis	31 (31.0)	32 (32.0)
Inferior extremity superficial thrombophlebitis	8 (8.0)	9 (9.0)
Superior extremity arterial thrombosis	5 (5.0)	5 (5.0)
Inferior extremity arterial thrombosis	5 (5.0)	5 (5.0)
Subclavian venous thrombosis	2 (2.0)	3 (3.0)
Superior extremity venous thrombosis	1 (1.0)	1 (1.0)
Neurologic manifestations		
Migraine	25 (25.0)	35 (35.0)
Stroke	10 (10.0)	10 (10.0)
Transient global amnesia	7 (7.0)	7 (7.0)
Acute ischaemic encephalopathy	5 (5.0)	6 (6.0)
Transient ischaemic attack	5 (5.0)	5 (5.0)
Epilepsy	4 (4.0)	4 (4.0)
Multiinfarct dementia	3 (3.0)	4 (4.0)
Chorea	1 (1.0)	1 (1.0)
Cerebellar ataxia	1 (1.0)	1 (1.0)
Cerebral venous sinus thrombosis	1 (1.0)	2 (2.0)
Transverse myelopathy	1 (1.0)	1 (1.0)
Cardiac manifestations		
Valve thickening/dysfunction	9 (9.0)	9 (9.0)
Vegetations	4 (4.0)	4 (4.0)
Acute cardiomyopathy	1 (1.0)	1(1.0)
Acute myocardial infaction	0 (0)	1 (1.0)
Pulmonary manifestations		
Pulmonary microthrombosis	7 (7.0)	7 (7.0)
Pulmonary embolism and infarction	5 (5.0)	5 (5.0)
Pulmonary artery thrombosis	2 (2.0)	2 (2.0)
Primary pulmonary hipertension	1 (1.0)	1 (1.0)
Acute respiratory distress syndrome	1 (1.0)	1 (1.0)
Fibrosing alveolitis	1 (1.0)	1 (1.0)
Renal and adrenal manifestations		
Renal vein thrombosis	1 (1.0)	1 (1.0)
Addison's syndrome	1 (1.0)	1 (1.0)
Hepatic and gastrointestinal manifestations		
Hepatic manifestations	4 (4.0)	4 (4.0)
Intestinal manifestations	4 (4.0)	5 (5.0)
Splenic manifestations	2 (2.0)	2 (2.0)
Pancreatic manifestations	1 (1.0)	1 (1.0)
Osteoarticular manifestations		
Osteonecrosis	2 (2.0)	2 (2.0)
Cutaneous manifestations		
Livedo reticularis	32 (32.0)	40 (40.0)
Skin ulcerations	14 (14.0)	14 (14.0)
Superficial cutaneous necrosis	10 (10.0)	10 (10.0)
Multiple subungueal splinter hemorrhage	9 (9.0)	9 (9.0)
Digital gangrene	3 (3.0)	3 (3.0)
Ophthalmologic manifestations		
Amaurosis fugax	11 (11.0)	11 (11.0)
Optic ischemic neuropathy	2 (2.0)	2 (2.0)
Retinal artery thrombosis	1 (1.0)	1 (1.0)
Hematologic manifestations		
Thrombocytopenia	27 (27.0)	28 (28.0)
Haemolytic anaemia	19 (19.0)	20 (20.0)

Table 2 shows the comparison of the main cumulated clinical manifestations between the 91 mestizo patients of this Latin American cohort and the 985 white patients (individuals with all white European ancestors) of the 'Euro-Phospholipid' cohort. Several clinical manifestations were more prevalent in Latin Americans and they included migraine, transient global amnesia, acute ischaemic encephalopathy, pulmonary microthrombosis, intestinal manifestations, *livedo reticularis*, skin ulcerations, superficial cutaneous necrosis, multiple subungual splinter hemorrhages, amaurosis fugax and haemolytic anaemia. Conversely, a few clinical manifestations were less prevalent in Latin Americans and they included stroke and pulmonary embolism.

A total of 66 patients (70.9% of the total female Latin American cohort) experienced one or more pregnancies (range, 1–23). Five patients (7.6% of pregnancies) presented pre-eclampsia/eclampsia. The most common fetal complications were early pregnancy losses (49.6% of pregnancies), premature live births

Table 2 Comparison of the main cumulated clinical manifestations between the 91 mestizo patients of the Latin American cohort and the 985 white patients of the 'Euro-Phospholipid' cohort

Manifestations	*Latin American patients No. (%)*	*'Euro-Phospholipid' cohort No. (%)*	*P*	*OR (95% CI)*
Peripheral thrombosis				
Inferior extremity deep vein thrombosis	29 (31.9)	385 (39.1)	NS	
Inferior extremity superficial thrombophlebitis	8 (8.8)	117 (11.9)	NS	
Superior extremity arterial thrombosis	5 (5.5)	26 (2.6)	NS	
Inferior extremity arterial thrombosis	5 (5.5)	43 (4.4)	NS	
Subclavian venous thrombosis	3 (3.3)	17 (1.7)	NS	
Neurologic manifestations				
Migraine	32 (35.2)	198 (20.1)	0.001	2.16 (1.33–3.49)
Stroke	9 (9.9)	195 (19.8)	0.017	0.44 (0.20–0.93)
Transient global amnesia	6 (6.69	7 (0.7)	0.0001	9.86 (2.86–33.56)
Acute ischemic encephalopathy	5 (5.5)	11 (1.1)	0.0001	5.15 (1.52–16.50)
Transient ischemic attack	5 (5.5)	109 (11.3)	NS	
Multiinfarct dementia	4 (4.4)	25 (2.5)	NS	
Epilepsy	4 (4.4)	68 (7.1)	NS	
Cardiac manifestations				
Valve thickening/dysfunction	9 (9.9)	114 (11.6)	NS	
Vegetations	4 (4.4)	27 (2.7)	NS	
Pulmonary manifestations				
Pulmonary microthrombosis	7 (7.7)	15 (1.5)	0.0001	5.39 (1.93–14.57)
Pulmonary embolism and infarction	4 (4.4)	137 (13.9)	0.011	0.28 (0.09–0.82)
Intraabdominal manifestations				
Hepatic manifestations	4 (4.4)	14 (1.4)	NS	
Intestinal manifestations	5 (5.5)	15 (1.5)	0.013	3.76 (1.16–11.39)
Splenic manifestations	2 (2.2)	11 (1.1)	NS	
Osteoarticular manifestations				
Osteonecrosis	2 (2.2)	23 (2.3)	NS	
Cutaneous manifestations				
Livedo reticularis	39 (42.9)	236 (24.0)	0.001	2.38 (1.50–3.78)
Skin ulcerations	14 (15.4)	55 (5.6)	0.001	3.06 (1.66–6.00)
Superficial cutaneous necrosis	10 (11.0)	21 (2.1)	0.0001	5.67 (2.40–13.17)
Multiple subungueal splinter hemorrhage	9 (9.9)	7 (0.7)	0.0001	15.33 (5.07–47.07)
Digital gangrene	3 (3.3)	32 (3.2)	NS	
Ophthalmologic manifestations				
Amaurosis fugax	11 (12.1)	53 (5.4)	0.024	2.42 (1.14–5.01)
Optic ischemic neuropathy	2 (2.2)	10 (1.0)	NS	
Hematologic manifestations				
Thrombocytopenia	28 (30.8)	286 (29.0)	NS	
Haemolytic anaemia	20 (22.0)	95 (9.6)	0.001	2.64 (1.48–4.66)
Obstetric manifestations*				
Pre-eclampsia/eclampsia	5 (7.6)	82 (13.9)	NS	
Fetal manifestations**				
Live births	119 (44.7)	753 (47.7)	NS	
Premature live births	20 (16.8)	80 (10.6)	NS	
Early pregnancy losses	132 (49.6)	560 (35.4)	0.0001	1.79 (1.37–2.35)
Late pregnancy losses	15 (5.6)	267 (16.9)	NS	
Fetal thrombosis	1 (0.4)	0 (0)	NS	

CI: confidence interval; NS: not significant; OR: odds ratio.
*66 pregnant women for Latin American patients group and 590 pregnant women for Europhospholipid cohort.
**266 pregnancies for Latin American patients group and 1580 pregnancies for Europhospholipid cohort.

(16.8% of pregnancies) and late pregnancy losses (5.6% of pregnancies). When compared with patients from the 'Euro-Phospholipid' cohort, Latin American patients had more early fetal losses (Table 2).

Immunologic features

The main immunological findings are summarized in Table 3. In the whole series, the aCL were detected in 88 (88%) patients and the LA in 40 (40%). In addition to aPL, some patients presented ANA (37%), anti-dsDNA (14%), anti-Ro (9%) and rheumatoid factor (11%), among other autoantibodies. No differences were found in the clinical presentation of the APS according to the presence or absence of these antibodies.

When compared with the white patients of the 'Euro-Phospholipid' cohort, the mestizo patients of the Latin American cohort presented a lower prevalence of IgG aCL (22.0% versus 43.7%; $P < 0.0005$; OR = 0.23; 95% CI = 0.11–0.32), LA (38.5% versus 53.2%; $P = 0.01$; OR = 0.15; 95% CI = 0.04–0.25), ANA (38.5% versus 59.9%; $P < 0.0005$; OR = 0.25; 95% CI = 0.10–0.32), anti-dsDNA (15.4% versus 28.9%; $P < 0.009$; OR = 0.14; 95% CI = 0.05–0.24), anti-RNP (0 versus 5.8%; $P = 0.04$; OR = 0.05; 95% CI = 0.007–0.10), and anti-Sm antibodies (0 versus 5.4%; $P = 0.03$; OR = 0.06; 95% CI = 0.01–0.11).

Discussion

Our study showed that several clinical manifestations were more prevalent in Latin Americans and they included migraine, transient global amnesia, acute ischaemic encephalopathy, pulmonary microthrombosis, intestinal manifestations, *livedo reticularis*, skin ulcerations, superficial cutaneous necrosis, multiple subungual splinter hemorrhages, amaurosis fugax and haemolytic anaemia. Conversely, a few clinical manifestations were less prevalent in Latin Americans and they included stroke and pulmonary embolism. In addition, the mestizo patients of the Latin American cohort presented a lower prevalence of IgG aCL, LA, ANA, anti-dsDNA, anti-RNP and anti-Sm antibodies.

Ethnicity is a social description assigned by individuals to themselves or others, usually based on a mix of heritage, culture and geography. Environmental as well as genetic factors contribute to ethnic variation and differences in disease patterns may be due to each one or both. A question that arises is whether the ethnic origin can modify the disease expression in patients with the APS.[9,10] Recently, the 'Euro-Phospholipid' project has analysed the clinical and immunologic manifestations of the APS in a large cohort of European patients (mainly Caucasian) and has defined several patterns of disease expression.[8] The current study analyses the APS in Latin American patients (mainly mestizos) using the same data-base protocol, thus allowing the comparison with the 'Euro-Phospholipid' cohort.

The 'Euro-Phospholipid' cohort consisted of 1,000 patients that have been gathered by a European consortium that was created in 1999 as part of the network promoted by the 'European Forum on aPL', a study group devoted to the development of multicenter projects with large populations of APS patients. These European patients were collected at 20 university centres that follow all the cases diagnosed in their referral areas in 13 European countries (Belgium, Bulgaria, Denmark, France, Germany, Greece, Hungary, Israel, Italy, the Netherlands, Portugal, Spain and UK), and include all sorts of APS manifestations. The Latin American cohort was gathered in two geographical areas (Mexico and Ecuador) and was derived by a wide variety of specialists and subspecialists from their referral areas.

Table 3 Comparison of the main immunologic features between the 91 mestizo patients of the Latin American cohort and the 985 white patients of the 'Euro-Phospholipid' cohort

Immunologic features	*Latin American patients No. (%)*	*'Euro-Phospholipid' cohort No. (%)*	*P*	*OR (95% CI)*
Anticardiolipin antibodies	80 (87.9)	868 (88.1)	NS	
IgG and IgM	50 (54.9)	317 (32.2)	<0.0005	0.22 (0.12–0.33)
IgG alone	20 (22.0)	430 (43.7)	<0.0005	0.23 (0.11–0.32)
IgM alone	10 (11.0)	121 (12.3)	NS	
Lupus anticoagulant	35 (38.5)	524 (53.2)	0.01	015 (0.04–0.25)
Alone	7 (7.7)	117 (11.9)	NS	
With anticardiolipin antibodies	28 (30.8)	407 (41.3)	NS	
Antinuclear antibodies	35 (38.5)	586 (59.5)	<0.0005	0.25 (0.10–0.32)
Anti-double-stranded DNA	14 (15.4)	292 (28.9)	<0.009	0.14 (0.05–0.24)
Anti-Ro/SSA	9 (9.9)	134 (13.6)	NS	
Anti-La/SSB	7 (7.7)	56 (5.7)	NS	
Rheumatoid factor	11 (12.1)	75 (7.6)	NS	
Anti-Sm	0	53 (5.4)	0.04	0.05 (0.007–0.10)
Anti-RNP	0	57 (5.8)	0.03	0.058 (0.01–0.11)

Although APS is being recognized with increasing frequency in medical practice, the diversity of its clinical and laboratory features makes precise diagnosis a real challenge for the clinician and this has been reflected in the present study. Overall, the prevalence of the major clinical features accepted as classification criteria[11] in the present cohort is comparable to that reported in previous studies.[4–7] Deep vein thrombosis (32.0%), stroke (10.0%), cutaneous necrosis (10.0%) and obstetric morbidity (including both fetal and maternal complications) were very common manifestations. However, several other manifestations that are considered 'minor' in the classification criteria were also frequently found, and these included *livedo reticularis*, migraine, thrombocytopenia, hemolytic anemia, amaurosis fugax, valve thickening/dysfunction and epilepsy, among others. Additionally, the present study allows a more precise estimate of the prevalence of a great variety of different clinical features that have occasionally been reported in some patients with the APS.[18,19] There are several clinical manifestations whose prevalence ranges between 1% and 5%, and these included arterial thrombosis in legs and arms, subclavian vein thrombosis, multiinfarct dementia, pulmonary microthrombosis, pulmonary hypertension, renal thrombosis and a variety of cutaneous lesions. Finally, this study confirms that the prevalence of some other reported manifestations, such as transverse myelopathy, Addison's syndrome, and pancreatic or hepatic manifestations, is very low (less than 1%). It should be emphasized that these prevalences are generally lower than those reported in earlier series and a possible reason for this fact is the systematic long-term use of anticoagulants for secondary prophylaxis of thrombotic events during the last decade.[5,22]

Interestingly, one of the most common clinical manifestations of the APS and, at the same time, a special characteristic among thrombophilic disorders is fetal morbidity. Additionally, maternal morbidity (mainly pre-eclampsia) is also relatively common in pregnant patients with APS. The most common fetal complications in our study – where 70.9% of the females experienced one or more pregnancies – were early fetal losses, premature birth, and late fetal losses, while the most common obstetric maternal complications was pre-eclampsia. However, it should be stressed that 74% of female patients who became pregnant in the present cohort succeeded in having one or more live births. This is one of the most important advances made in the last decade after the close follow-up and medical awareness of these patients together with the widespread use of antiaggregant and anticoagulant drugs (mainly, low dose aspirin and low molecular weight heparin) and the careful monitoring of these pregnancies.[23]

The frequencies of the major immunological features of APS in the present series are also comparable to other reports.[4–7] In addition to aPL, ANA were detected at some time during the course of the illness, but usually at low titers, and high titers of anti-dsDNA antibodies were found in patients with associated SLE.

Genetic risk factors for aPL and APS have been studied in several ethnic and geographic populations.[24] The etiology of the APS is linked to genetic predisposition, which may be accounted for by genes of the major histocompatibility complex.[10] The association of several HLA class II gene polymorphisms and APS has been reported in a number of studies from different areas of the world, summarized in a recent review.[10] This association, probably along with other genetic factors like polymorphisms of HLA-DM molecules[25] or β_2-glycoprotein I gene,[26] may determine the development of different aspects of the disease.[27] Unfortunately, HLA data of both groups of patients was unavailable in this study.

It is of interest the finding that several clinical manifestations were significantly more prevalent in Latin American mestizo patients than in European white patients, and they included mainly neurological and cutaneous manifestations as well as hemolytic anemia. There are several possible reasons for these differences in disease manifestations between Latin American and European patients and they include environmental and socioeconomic factors (access to primary medical care, the threshold for referral from primary to secondary care, prevalence of traditional vascular risk factors in case of cerebrovascular events, and therapy). However, genetic factors cannot be excluded. This has been demonstrated in the field of SLE where, both genetic and socioeconomic determinants, as well as other factors associated with patients' ethnicity have been related with the presentation of the disease.[28,29]

There are some limitations to the present study. First, mestizo patients analysed were only representative of Latin American patients from two countries (Mexico and Ecuador). Thus, the data cannot be considered representative of all Latin American patients' population. Second, although this study is a prospective analysis of clinical and immunologic features of APS patients, the clinical data from disease presentation were obtained from the medical records. Third, it was not the objective of this study to analyze the sociodemographic data from both cohorts. Some differences (early pregnancy losses) may relate only to access and quality of care of patients.

In conclusion, this study has shown the prevalence and characteristics of the main clinical and immunological manifestations at the onset and during the evolution of the APS in a well defined cohort of patients from Latin America, mainly of mestizo origin. It is

possible that the ethnic origin, in addition to environmental and socioeconomic factors, can modify the disease expression. This should prompt a search for genetic factors that affect the pathogenesis of APS, as well other sociodemographic determinants that may affect the presentation of this disease.

References

1 Asherson RA, Cervera R, Piette JC, Shoenfeld Y. Milestones in the antiphospholipid syndrome. In Asherson RA, Cervera R, Piette JC, Shoenfeld Y eds. *The antiphospholipid syndrome II-Autoimmune Thrombosis*. Elsevier, 2002: 3–9.
2 Font J, López-Soto A, Cervera R *et al.* The 'primary' antiphospholipid syndrome: Antiphospholipid antibody pattern and clinical features of a series of 23 patients. *Autoimmunity* 1991; **9**: 69–75.
3 Asherson RA, Cervera R, Piette JC *et al.* Catastrophic antiphospholipid syndrome: Clues to the pathogenesis from a series of 80 patients. *Medicine (Baltimore)* 2001; **80**: 355–377.
4 Alarcón-Segovia D, Delezé M, Oria CV *et al.* Antiphospholipid antibodies and the antiphospholipid syndrome in systemic lupus erythematosus. A prospective analysis of 500 consecutive patients. *Medicine (Baltimore)* 1989; **68**: 353–365.
5 Muñoz-Rodríguez FJ, Font J, Cervera R *et al.* Clinical study and follow-up of 100 patients with the antiphospholipid syndrome. *Semin Arthritis Rheum* 1999; **29**: 182–190.
6 Vianna JL, Khamashta MA, Ordi-Ros J *et al.* Comparison of the primary and secondary antiphospholipid syndrome. A European multicenter study of 131 patients. *Am J Med* 1994; **96**: 3–9.
7 Asherson RA, Khamashta MA, Ordi-Ros J *et al.* The "primary" antiphospholipid syndrome: major clinical and serological features. *Medicine (Baltimore)* 1989; **68**: 366–374.
8 Cervera R, Piette JC, Font J *et al.* Antiphospholipid syndrome: Clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. *Arthritis Rheum* 2002; **46**: 1019–1027.
9 Wilson WA. Ethnicity and APS. *J Autoimmun* 2000; **15**: 153–155.
10 Uthman I, Khamashta M. Ethnic and geographical variation in antiphospholipid (Hughes) syndrome. *Ann Rheum Dis* 2005; **64**: 1671–1676.
11 Wilson WA, Gharavi AE, Koike T *et al.* International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. *Arthritis Rheum* 1999; **42**: 1309–1311.
12 Tan EM, Cohen AS, Fries J *et al.* The 1982 revised criteria for classification of systemic lupus erythematosus. *Arthritis Rheum* 1982; **25**: 1271–1277.
13 Arnett FC, Edworthy SM, Bloch DA *et al.* The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; **31**: 315–324.
14 Bohan A, Peter JB. Polymyositis and dermatomyositis. *N Engl J Med* 1975; **292**: 344–347.
15 Subcommittee for scleroderma criteria of the American Rheumatism Association diagnostic and therapeutic criteria committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). *Arthritis Rheum* 1980; **23**: 581–590.
16 Vitali C, Bombardieri S, Moutsopoulos HM *et al.* Preliminary criteria for the classification of Sjögren's syndrome. Results of a prospective concerted action supported by the European Community. *Arthritis Rheum* 1993; **36**: 340–347.
17 Hunder GG, Arend WP, Bloch DA *et al.* The American College of Rheumatology 1990 criteria for the classification of vasculitis. *Arthritis Rheum* 1990; **33**: 1065–1144.
18 Asherson RA, Cervera R, Piette JC, Shoenfeld Y eds. *The antiphospholipid syndrome II-Autoimmune Thrombosis*. Elsevier, 2002.
19 Ad hoc committee on classification of headaches. Classification and diagnostic criteria for headaches disorders, cranial neuralgias and facial pain. *Cephalalgia* 1988; **8**(Suppl 7): 8–96.
20 Harris EN, Gharavi AE, Patel SP, Hughes GRV. Evaluation of the anti-cardiolipin antibody test: report of an international workshop held 4 April 1986. *Clin Exp Immunol* 1987; **68**: 215–222.
21 Brandt JT, Triplett DA, Alving B, Scharrer I. Criteria for the diagnosis of lupus anticoagulants: an update. *Thromb Haemost* 1995; **74**: 1185–1190.
22 Khamashta MA, Cuadrado MJ, Mujic F, Taub NA, Hunt BJ, Hughes GRV. The management of thrombosis in the antiphospholipid-antibody syndrome. *N Engl J Med* 1995; **332**: 993–997.
23 Derksen RHWM, Khamashta MA, Branch DW. Management of the obstetric antiphospholipid syndrome. *Arthritis Rheum* 2004; **50**: 1028–1039.
24 Wilson WA, Gharavi AE. Genetic risk factors for aPL syndrome. *Lupus* 1996; **5**: 398–403.
25 Sanchez ML, Katsumata K, Atsumi T *et al.* Association of HLA-DM polymorphism with the production of antiphospholipid antibodies. *Ann Rheum Dis* 2004; **63**: 1645–1648.
26 Yasuda S, Atsumi T, Matsuura E *et al.* Significance of valine/leucine247 polymorphism of beta2-glycoprotein I in antiphospholipid syndrome: increased reactivity of anti-beta2-glycoprotein I autoantibodies to the valine 247 beta2-glycoprotein I variant. *Arthritis Rheum* 2005; **52**: 212–218.
27 Caliz R, Atsumi T, Kondeatis E *et al.* HLA class II gene polymorphisms in antiphospholipid syndrome: haplotype analysis in 83 Caucasoid patients. *Rheumatology* 2001; **40**: 31–36.
28 Reveille JD, Moulds JM, Ahn Ch. Systemic lupus erythematosus in three ethnic groups. The effects of HLA class II, C4, and CR1 alleles, socioeconomic factors, and ethnicity at disease onset. *Arthritis Rheum* 1998; **41**: 1161–1172.
29 Alarcon GS, Rodriguez JL, Benavides G. Systemic lupus erythematosus in three ethnic groups. Acculturation, health-related attitudes and behaviors, and disease activity in Hispanic patients from the LUMINA cohort. *Arthritis Care Research* 1999; **12**: 267–274.