Abstract

Objective: To analyze the demographic, clinical, and laboratory characteristics of catastrophic antiphospholipid syndrome (CAPS) patients with cardiac involvement, and to identify the factors associated with this cardiac involvement.

Material and Methods: Based on the analysis of the "CAPS Registry", the demographic, clinical, and serological characteristics of patients with cardiac involvement were analyzed. Cardiac involvement was defined as heart failure, valvular disease, acute myocardial infarction, pericardial effusion, pulmonary arterial hypertension, systolic dysfunction, intracardiac thrombosis, and microvascular disease. Univariate and multivariate analysis was used for multiple comparisons.

Results: 749 patients (293 [39%] women and mean age 38.1 ± 16.2 years) accounting for 778 CAPS events were included, of them 404 (52%) had cardiac involvement. The main cardiac manifestations were heart failure in 185/377 (55%), valve disease in 116/377 (31%), and acute myocardial infarction in 104/378 (28%). Of 58 patients with autopsy/biopsy, 48 (83%) had cardiac thrombotic microangiopathy, Stroke (29% vs. 21%, p = 0.012), transient cerebral vascular accident (2% vs. 1%, p = 0.005), pulmonary infarction (26% vs. 3%, p = 0.017), renal infarction (46% vs. 35%, p = 0.006), acute kidney injury (70% vs. 53%, p <0.001), and livedo reticularis (24% vs. 17%, p = 0.016) were significantly more frequent during CAPS events with versus without heart involvement. Multivariate analysis identified acute kidney injury (OR 1.068, IC 95% 1.8-4.8, p <0.001) as the only clinical characteristics that were, independently, associated with cardiac involvement in CAPS events. Cardiac involvement was not related to higher mortality.

Conclusions: Cardiac involvement is frequent in CAPS, with association with kidney involvement, and it is not related to higher mortality. The presence of cardiac microthrombosis was demonstrated in most biopsies/autopsies performed.

Keywords

Catastrophic antiphospholipid syndrome, cardiac involvement, antiphospholipid syndrome, valve involvement, antiphospholipid antibodies, lupus anticoagulant

1. Introduction

Classically, the antiphospholipid syndrome (APS) was defined by the development of venous and/or arterial thrombosis, often multiple, and pregnancy morbidity in patients with antiphospholipid antibodies (aPL), namely lupus anticoagulant (LA), anticardiolipin antibodies (aCL), and/or anti-β2 glycoprotein-I (β2GPI) antibodies [1]. Very recently, the 2023 ACR/EULAR APS Classification Criteria were published, encompassing six clinical and two laboratory domains [2].

Heart valve involvement (thickening and/or vegetation), one of the domains of the new classification criteria, has a prevalence of 11.6% in large cohorts of patients with APS [3]. In the Europhospholipid project cohort, valve thickening/dysfunction were observed in 4.6% of 1000 APS patients during a prospective follow-up of 10 years [4].

Approximately 1% of APS patients develop a severe form of APS defined by: a) clinical evidence of multiple organ involvement developing over a short period of time; b) histopathological evidence of small vessel occlusions; and c) laboratory confirmation of aPL [5]. In the first descriptions of this devastating type of APS, the mortality was 50%. Due to this poor prognosis, the term “catastrophic” was introduced to describe this life-threatening form of APS (CAPS) [6].

Based on a descriptive analysis of approximately 500 CAPS patients, the heart was one of the most affected organs, reaching a prevalence of 50%, in the form of ischemic heart disease, valvulopathy, heart failure, and/or non-bacterial thrombotic endocarditis [7]. Recent studies have suggested that cardiac involvement in thrombotic critically ill APS patients is associated with a worse prognosis [8].

The present study aims to describe the demographic, clinical and laboratory characteristics, precipitating factors, treatment strategies, and outcomes of CAPS patients with cardiac involvement included in the “CAPS Registry”.

2. Material and Methods

We performed a retrospective cross-sectional study that included all patients enrolled in the "CAPS Registry", a registry developed in 2000 by the European Forum on Antiphospholipid Antibodies [5, 9]. This database contains data collected from patients with CAPS between April 1992 to August 2023. Patients in the "CAPS Registry" were personally reported to the registry coordinators by their physicians or included based on published reports. Data standardization was achieved through the utilization of anonymous data collection forms. Published case reports are identified through periodic systematic reviews of PubMed. All patients met the current classification criteria for definite or probable CAPS [10]. The “CAPS Registry” project obtained approval from the ethical committee for clinical research at Hospital Clinic, Barcelona.

Systematic data collection includes demographic variables (gender, age, diagnosis of the underlying disorder), precipitating factors, main clinical manifestations, immunologic features, histologic and imaging technique findings, treatment, and outcome. Patients with definite and probable CAPS classification (those with evidence of involvement of at least two organs in a short period of time with laboratory evidence of circulating aPL) were included in this review [5].

In this retrospective analysis, CAPS patients with cardiac involvement were compared with patients without cardiac involvement. Cardiac involvement was defined as the presence of heart failure, valvular disease, acute myocardial infarction, pericardial effusion, pulmonary arterial hypertension, systolic dysfunction, intracardiac thrombosis, and microvascular disease. Heart failure and acute myocardial infarction were defined, according to the definitions in the most recent consensus [11,12]. Pericardial effusion, pulmonary arterial hypertension, systolic dysfunction, intracardiac thrombosis and microvascular disease were recorded according to the authors' description in each case. When available, biopsies or necropsies of CAPS patients with cardiac involvement have also been analyzed, as well as echocardiographic data and hemodynamic studies.

The statistical analysis was performed with SPSS statistical software (version 23.0) and considering the CAPS episodes. Continuous variables were reported as mean value with 95% confidence interval (IC 95%) while frequency as a percentage for categorical variables. T-test was calculated to detect differences between groups in continuous variables while ANOVA was used when more than two groups existed. Chi-square was performed to evaluate differences between categorical data and Fisher's exact tests when the former was not applicable. For multivariate analysis, logistic regression was used with Bonferroni correction for multiple comparisons. All statistical tests were two-tailed and only differences with a p value less than 0.05 were considered statistically significant.

3. Results

3.1. General characteristics

Overall, we identified 765 patients, but 16 were excluded because no data of cardiac involvement were available. Of remaining 749, 725 (97%) had a single CAPS episode, 19 (33%) had two, and five (0.7%) had three, accounting for a total of 778 events. Of them, 404 (52%) had cardiac involvement. One hundred and ten (27%) events occurred in patients with a previous diagnosis of systemic lupus erythematous (SLE) and 175 (43%) with primary APS (PAPS).

3.2. Type of cardiac involvement

3.2.1. Cardiac manifestations

The main cardiac manifestations were heart failure present in 185 (49%) events, valve involvement in 116 (31%), and acute myocardial infarction in 104 (27%). Considering valve heart disease, mitral in 55/124 (44%) and aortic 20/124 (16%) valves were the most frequently affected, with a predominant functional alteration in the form of regurgitation, 36/55 (65%) in the mitral valve and 12/20 (60%) in the aortic valve. Fifty-six (14%) events presented with Libman-Sacks endocarditis [13], mostly on the mitral valve present in 11 (61%) events. All cardiac manifestations are shown in Table 1.

3.2.2. Imaging technique findings

Data from echocardiography were available in 124 (16%) events being normal in 61 (49%) of them (Table 1). Ejection fraction (<40%) was decreased in 56 (45%).

Coronary angiography was only performed in 29 (3.7%) events; mostly without angiographically significant lesions, but in only 6 (20.7%) events a coronary artery disease of one vessel was disclosed (Table 1)

3.2.2. Histologic findings

Cardiac tissue samples were available only in 58 (14.4%) events. Cardiac thrombotic microangiopathy was the most frequent finding described in histological samples, present in 48 (82.8%) of them. The description of the cardiac pathological samples is shown in Table 2.

In episodes of cardiac involvement of CAPS with the histological finding of thrombotic microangiopathy, the most frequent clinical manifestation was systolic dysfunction present in 46.7% (7/15) followed by heart failure in 40% (18/45), valve involvement in 38.6% (17/44), nonbacterial thrombotic endocarditis in 35.7% (15/42), and acute myocardial infarction in 24.4% (10/41) of the episodes. The presence of pericardial effusion and pulmonary arterial hypertension (PAH) were recorded in 12.5% (2/16) and 8.3% (1/12) of the episodes in which this information was available.

3.3. Features associated with cardiac involvement

The previous diagnosis of PAPS (43% versus 54%, p = 0.003) and the presence of neoplasia (6% versus 11%, p = 0.021) or consumption of oral contraceptives (3% versus 8%, p = 0.011), as precipitating factors, were less frequent during CAPS events with cardiac involvement, compared with those without cardiac involvement (Table 3).

Stroke (29% versus 21%, p = 0.012), transient cerebral vascular accident (2% versus 1%, p = 0.005), pulmonary infarction (26% versus 3%, p = 0.017), renal infarction (46% versus 35%, p = 0.006), acute kidney injury (70% versus 53%, p <0.001) and livedo reticularis (24% versus 17%, p = 0.016) were significantly more frequent in CAPS events with cardiac involvement. In contrast, digital gangrene (8% versus 3%, p = 0.001), gastrointestinal bleeding (7% versus 3%, p = 0.026), paralytic ileus (3% versus 0.8%, p = 0.028) and histological findings of intestinal

thrombotic microangiopathy (36% versus 19%, p = 0.036) were more frequent in CAPS events without cardiac involvement. No statistically significant differences were found in mortality between the two groups (Table 4).

There was no difference between single/double/triple positivity between events with or without cardiac involvement. Supplementary Table S1 shows all the laboratory features and aPL profiles analyzed in patients according to the presence of cardiac involvement.

In CAPS episodes with cardiac involvement, we have tried to identify whether the aPL profile and the presence of laboratory data suggestive of thrombotic microangiopathy (thrombocytopenia, hemolysis parameters, and the presence of schistocytes) could be related to any specific clinical manifestation or with systolic dysfunction observed by echocardiogram (Supplementary Table S2). Only the isolated positivity of LA, in the acute phase of CAPS event, was related to the presence of valve involvement (45% versus 28%, p = 0.12), while the rest of the aPL profile and the analytical data suggestive of thrombotic microangiopathy were not related to any of the cardiac manifestations.

One hundred and ten (27%) events occurred in patients with a previous diagnosis of SLE. In this group, valve involvement (41% versus 27%, p = 0.009) was more frequent than in patients without a prior diagnosis of SLE, while acute myocardial infarction (19% versus 31%, p = 0.028%) was more frequent in those without previous SLE diagnosis. Supplementary Table S3 shows the frequencies of different cardiac manifestations according to a prior diagnosis of SLE.

Antiplatelet therapy (18% versus 12%, p = 0.022) was the only treatment used more frequently in CAPS patients with cardiac involvement, with no differences in the frequency of use of other treatments. This treatment was always performed in combination with at least one other treatment, with anticoagulation being the most common, in 60/67 (89.5%) CAPS events.

The different treatments received, including immunosuppressive therapy, biological treatment, and haemodialysis, are descripted in the Supplementary Table S4.

Multivariate analysis using the variables with significant results in the univariate analysis identified acute kidney injury (OR 1.068, IC 95% 1.8-4.8, p <0.001) as the only clinical characteristic that were, independently, significant statistically associated with cardiac involvement in CAPS events. On the other hand, the presence of paralytic ileus (OR -2.413, IC 95% 0.01-0.77, p 0.028) was independently associated with the group of CAPS events without cardiac involvement (Supplementary Table S5).

4. Discussion

Our analysis of the CAPS registry demonstrated that 404/778 (52%) of CAPS events patients have cardiac involvement in the form of heart failure in 185/377 (55%), valve disease in

116/377 (31%), and acute myocardial infarction in 104/378 (28%). Cardiac involvement was already described for the first time in cases and series of patients with PAPS and heart valve involvement in the early years of the 1990s [14–20], when two-dimensional and Doppler echocardiography studies revealed a 32% to 38% prevalence of valvular defect. Since then, numerous authors have reported their experience describing different clinical [21-23] and analytical associations [23-28] with valve involvement in patients with APS, as well as their evolution or response to different treatments [21, 23-25, 30-32]. If fact, cardiac involvement in APS has been included in the recent 2023 ACR/EULAR APS classification criteria [2] as: a) established microvascular myocardial disease (5 points); and b) valve disease (2 points for thickening and 4 for vegetation).

Considering its multiorgan involvement as well as its clinical severity, a more detailed description of cardiac involvement in CAPS patients is less common. Even so, different authors have published their experience with valve involvement [33-38], heart failure and/or cardiogenic shock [39-46], and intracardiac thrombosis [47-51]. There are some cases described with ST-segment elevation myocardial infarction with non-obstructive coronary arteries [52] and sudden death as the only cardiac manifestation of CAPS [53]. Like previous studies, we have found a high frequency of cardiac involvement (>50%) in the 778 CAPS events registered to date in the CAPS Registry. Its predominant effects have also been described in the form of heart failure, valve involvement and acute myocardial infarction, being the pericardial effusion, echocardiographic findings of PAH, Libman-Sacks endocarditis, and intracavitary thrombosis, less frequent findings.

A recent review on valve disease in autoimmune diseases [54] concluded that that the presence of antiphospholipid antibodies increases the risk of valvular disease and thrombotic complications in these patients, with thickened and fibrous valves being the most frequent findings, and mitral and aortic regurgitation as the most common sequelae. These two disorders, together with tricuspid regurgitation, are also valvular diseases more frequent in our cohort, and cerebral, pulmonary, and renal embolic complications have been related to cardiac involvement in our patients.

Microvascular myocardial involvement without epicardial macrovascular distribution has been described in APS patients [55], suggesting the presence of myocardial thrombotic microangiopathy with a highly variable spectrum of clinical manifestations. In the previously described cases of cardiac involvement in CAPS, only anatomopathological samples were described in two of them [41,43], showing thrombotic microangiopathy. In our review, histopathological confirmation of the occlusion of a small vessel at the cardiac level, as a classifying criterion for CAPS, was obtained in 83% of the cardiac anatomopathological samples analyzed, indicating the presence of thrombotic microangiopathy. It is important to note that cardiac tissue was available in only 11% of cardiac CAPS events. This may represent a selection bias for the most serious events and may not be extrapolated to all cardiac CAPS. Even with this fact, the findings described could justify the etiology of heart failure or ischemic cardiomyopathy,

being mediated by microcirculation involvement. It presents with normal coronary arteries, and although it can be suspected by a Doppler echocardiographic study, its confirmation requires cardiac magnetic resonance, which has superior performance to perfusion studies with single-photon emission computed tomography (SPECT).

Some authors have reported a differentiated clinical profile of patients with APS and cardiac involvement [56-58], highlighting a higher frequency of arterial thrombotic events, cardiovascular risk factors and cutaneous and neurological involvement, mainly livedo reticularis and stroke. Unlike what happened with APS, to date there is no described association between the presence of cardiac involvement in CAPS and other clinical manifestations. The present analysis from the data of CAPS Registry shows a significant association between cardiac involvement and the presence of stroke and transient ischemic attack, probably greatly influenced by valve involvement and embolic phenomena. Pulmonary and kidney ischemic involvement, and acute kidney injury, were also more frequent in patients with cardiac involvement, again in the context of probable emboligenic phenomena +/- hemodynamic instability and tissue hypoperfusion due to the severity of the disease itself. On the contrary, skin involvement in the form of gangrene and gastrointestinal involvement, with bleeding, paralytic ileus, and findings of gastrointestinal thrombotic microangiopathy, were more frequent in patients with CAPS without cardiac involvement. However, these differences were minimized in the multivariate analysis, with transient cerebral vascular accident and acute kidney injury as the clinical characteristics associated with patients with CAPS and cardiac involvement, and only the presence of paralytic ileus as a clinical finding associated with CAPS patients without cardiac involvement.

During the 10-year follow-up of 1000 patients with APS [4], myocardial infarction was second cause of death, occurring in 13.9% of the patients. In the previous analysis of all patients in the CAPS registry [7], those who previously had a diagnosis of SLE had higher mortality along with a higher frequency of cardiac, cerebral, and cranial events. However, as previous studies have reported [8], we do not find significant differences in terms of mortality between patients with and without cardiac involvement.

In patients with cardiac CAPS, LA, IgG aCL and IgG aβ2GPI antibodies were the most often implicated aPL (83%, 77% and 78% respectively). This pattern of antibodies is like that described in the overall CAPS series, without differences between the groups with cardiac involvement [7]. Isolated LA positivity was associated to an increased prevalence of valve involvement. However, these data probably cannot be considered reliable or useful, since not all patients were tested to detect the three aPL and, probably, some of the LA determinations were made under decoagulant treatment. Added to these limitations is the fact that current guidelines recommend avoiding LA determination in patients during acute thrombotic events [59], since some of the coagulation factors are also acute phase reactive and, therefore, increase during acute thrombosis.

The positivity in one or more antibody patterns was not related to other types of cardiac involvement such as acute myocardial infarction or systolic ventricular dysfunction. Analytical parameters compatible with thrombotic microangiopathy such as thrombocytopenia, hemolytic anemia and/or presence of schistocytes were not related to any of the cardiac conditions. The lack of association of any cardiac involvement with thrombotic microangiopathy parameters even though this is the most common histological lesion can be explained by the low number of samples available and by the fact that thrombotic microangiopathy parameters were not available in all CAPS episodes. Furthermore, in some cases, the information available was according to the criteria of each author.

In our series, prior diagnosis of SLE has been related to a higher frequency of valvular involvement in CAPS cardiac events, suggesting a dual etiopathogenic mechanism of valvular injury. However, these results should be interpreted with caution due to the limitations in aPL determination mentioned above.

The retrospective nature of the registry, the participation of numerous groups of different nationalities in it, and the fact that not all variables are recorded in each CAPS event are the main limitations of this study. This heterogeneous approach to patients with CAPS entails a difficulty in the organization of information and probably leading to some reporting and publication bias, as our cohort is established primarily based on reports or case series. Another limitation of the study is that, in the CAPS registry, the presence of previous heart disease is not recorded. Therefore, we could not identify a subgroup of patients with CAPS more susceptible to suffering cardiac events due to previous pathology, beyond the event itself. In summary, the present study is based on existing knowledge in CAPS with the largest cohort of cases published to date. Despite several limitations of the CAPS Registry, it represents an image of the real world and offers a complete perspective of the disease. Therefore, cardiac involvement is frequent in CAPS, with histological involvement such as thrombotic microangiopathy, with a certain association with brain, lung, and kidney involvement. On the contrary, the previous diagnosis of PAPS and gastrointestinal involvement would act as a protective factor for cardiac involvement in CAPS.

5. Conclusions

Cardiac involvement is a frequent manifestation of CAPS, mainly as heart failure, valvular involvement, and acute myocardial infarction, and it is not related to higher mortality. It is more frequent in patients with PAPS and clinically associated to neurological involvement, and pulmonary and renal infarcts The presence of cardiac microthrombosis was demonstrated in most biopsies/autopsies performed.

Disclosure statement

The authors have declared no conflicts of interest.

Data availability

The authors confirm that the data supporting the findings of this study are available within the article.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

None

References

[1] Cervera R. Antiphospholipid syndrome. Thromb Res 2017;151 Suppl 1:S43-S47.
[2] Barbhaiya M, Zuily S, Naden R, et al. ACR/EULAR APS Classification Criteria Collaborators. 2023 ACR/EULAR antiphospholipid syndrome classification criteria. Ann Rheum Dis 2023;82:1258-1270.
[3] 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.
[4] Cervera R, Serrano R, Pons-Estel GJ,et al. Morbidity and mortality in the antiphospholipid syndrome during a 10-year period: a multicentre prospective study of 1000 patients. Ann Rheum Dis 2015;74:1011-8.
[5] 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.
[6] Asherson RA. The catastrophic antiphospholipid (Asherson's) syndrome. Autoimmun Rev 2006;6:64-7.
[7] Rodríguez-Pintó I, Moitinho M, Santacreu I, et al. Catastrophic antiphospholipid syndrome (CAPS): Descriptive analysis of 500 patients from the International CAPS Registry. Autoimmun Rev 2016;15:1120-1124.
[8] Azoulay LD, Pineton de Chambrun M, Larcher R, et al. Prevalence, characteristics and outcome of cardiac manifestations in critically-ill antiphospholipid syndrome patients. J Autoimmun 2022;133:102908.
[9] Erkan D, Espinosa G, Cervera R. Catastrophic antiphospholipid syndrome: updated diagnostic algorithms. Autoimmun Rev 2010;10:74-9.

[10] Cervera R, Font J, Gómez-Puerta JA, et al. 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.
[11] Bozkurt B, Coats AJ, Tsutsui H, et al. Universal Definition and Classification of Heart Failure: A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. J Card Fail 2021;1:S1071-9164(21)00050-6.
[12] Thygesen K, Alpert JS, Jaffe AS, et al. Fourth Universal Definition of Myocardial Infarction (2018). J Am Coll Cardiol 2018;72:2231-2264.
[13] Ibrahim AM, Siddique MS. Libman-Sacks Endocarditis. StatPearls [Internet]. Treasure Island (FL): StatPearls; 2023.
[14] Vianna JL, Khamashta MA, Ordi-Ros J, et al. Comparison of the primary and secondary antiphospholipid syndrome: a European Multicenter Study of 114 patients. Am J Med 1994;96:3-9.
[15] Barbut D, Borer JS, Wallerson D, Ameisen O, Lockshin M. Anticardiolipin antibody and stroke: possible relation of valvular heart disease and embolic events. Cardiology 1991;79:99-109.
[16] Kalashnikova LA, Nasonov EL, Borisenko VV, et al. Sneddon's syndrome: cardiac pathology and antiphospholipid antibodies. Clin Exp Rheumatol 1991;9:357-61.
[17] Font J, Cervera R, Paré C, et al. Non-infective verrucous endocarditis in a patient with 'primary' antiphospholipid syndrome. Br J Rheumatol 1991;30:305-7.
[18] Brenner B, Blumenfeld Z, Markiewicz W, Reisner SA. Cardiac involvement in patients with primary antiphospholipid syndrome. J Am Coll Cardiol 1991;18:931-6.
[19] Cervera R, Khamashta MA, Font J, et al. High prevalence of significant heart valve lesions in patients with the 'primary' antiphospholipid syndrome. Lupus 1991;1:43-7.
[20] Galve E, Ordi J, Barquinero J, et al. Valvular heart disease in the primary antiphospholipid syndrome. Ann Intern Med 1992;116:293-8.
[21] Pardos-Gea J, Ordi-Ros J, Avegliano G, et al. Echocardiography at diagnosis of antiphospholipid syndrome provides prognostic information on valvular disease evolution and identifies two subtypes of patients. Lupus 2010;19:575-82.
[22] Krause I, Lev S, Fraser Aet al. Close association between valvar heart disease and central nervous system manifestations in the antiphospholipid syndrome. Ann Rheum Dis 2005;64:1490-3.
[23] Pons I, Louro J, Sitges M, et al. Heart Valve Involvement in Patients with Antiphospholipid Syndrome: A Long-Term Follow-Up Study of a Single Centre. J Clin Med 2023;12:2996..
[24] Perez-Villa F, Font J, Azqueta M, et al. Severe valvular regurgitation and antiphospholipid antibodies in systemic lupus erythematosus: a prospective, long-term, followup study. Arthritis Rheum 2005;53:460-7.
[25] Cieśla M, Wypasek E, Undas A. IgA Antiphospholipid Antibodies and Anti-Domain 1 of Beta 2 Glycoprotein 1 Antibodies are Associated with Livedo Reticularis and Heart Valve Disease in Antiphospholipid Syndrome. Adv Clin Exp Med 2014;23:729-33.
[26] Djokovic A, Stojanovich L, Kontic M, Stanisavljevic N, Radovanovic S, Marisavljevic D. Association between cardiac manifestations and antiphospholipid antibody type and level in a cohort of Serbian patients with primary and secondary antiphospholipid syndrome. Isr Med Assoc J 2014;16(3):162-7.
[27] Zuily S, Regnault V, Selton-Suty C, et al. Increased risk for heart valve disease associated with antiphospholipid antibodies in patients with systemic lupus erythematosus: meta-analysis of echocardiographic studies. Circulation 2011;124:215-
[28] Turiel M, Sarzi-Puttini P, Peretti R, et al. Five-year follow-up by transesophageal echocardiographic studies in primary antiphospholipid syndrome. Am J Cardiol 2005;96:574-9.

[29] Vivero F, Gonzalez-Echavarri C, Ruiz-Estevez B, Maderuelo I, Ruiz-Irastorza G. Prevalence and predictors of valvular heart disease in patients with systemic lupus erythematosus. Autoimmun Rev 2016;15:1134-1140.
[30] Espínola-Zavaleta N, Vargas-Barrón J, Colmenares-Galvis T, et al. Echocardiographic evaluation of patients with primary antiphospholipid syndrome. Am Heart J 1999;137:973-8.
[31] Zavaleta NE, Montes RM, Soto ME, Vanzzini NA, Amigo MC. Primary antiphospholipid syndrome: a 5-year transesophageal echocardiographic followup study. J Rheumatol 2004;31:2402-7.
[32] Kampolis C, Tektonidou M, Moyssakis I, et al. Evolution of cardiac dysfunction in patients with antiphospholipid antibodies and/or antiphospholipid syndrome: a 10-year follow-up study. Semin Arthritis Rheum 2014;43:558-65.
[33] Rato IR, Barbosa AR, Afonso DJ, Beça S. Catastrophic antiphospholipid syndrome presented as ruptured papillary muscle during puerperium in a patient with systemic lupus erythematosus. Lupus 2021;30:1017-1021.
[34] Grinberg A, Midlij M, Tiosano B, Shreter R, Kesler A. Neovascular Glaucoma as a Presenting Sign of Catastrophic Antiphospholipid Syndrome with a “Catastrophic” Heart Valve Finding. Case Rep Ophthalmol 2021;12:664-669.
[35] Millan-Iturbe O, Aguilar-De La Torre DL, Sauza-Sosa JC, Camarena-Alejo G. MitraClip Detachment and Recapture in a Patient With Catastrophic Antiphospholipid Syndrome. JACC Cardiovasc Interv 2019;12:e211-e213.
[36] Teunisse CC, Kalsbeek AJ, de Vries ST, et al. Reversible cardiac valvular disease in catastrophic antiphospholipid syndrome. Neth J Med 2010;68:215-20.
[37] Zakynthinos EG, Vassilakopoulos T, Kontogianni DD, Roussos C, Zakynthinos SG. A role for transoesophageal echocardiography in the early diagnosis of catastrophic antiphospholipid syndrome. J Intern Med 2000;248:519-24.
[38] Yamamoto H, Iwade T, Nakano R, et al. Images in cardiovascular medicine. Numerous small vegetations revealing Libman-Sacks endocarditis in catastrophic antiphospholipid syndrome. Circulation 2007;116:e531-5.
[39] Elmusa E, Raza MW, Muneeb A, Zahoor H, Naddaf N. Catastrophic Antiphospholipid Syndrome: A Rare Cause of Acute Heart Failure. Cureus 2023;15:e42012.
[40] Mittal N, Abohelwa M, Rahman MR, Shurmur S. Cardiovascular complications of catastrophic antiphospholipid syndrome: a case report and review of literature. Eur Heart J Case Rep 2022;6:ytac199.
[41] Lai AC, Feinman J, Oates C, Parikh A. A case report of acute heart failure and cardiogenic shock caused by catastrophic antiphospholipid syndrome and lupus myocarditis. Eur Heart J Case Rep 2022;6(:ytac446.
[42] Hermel M, Hermel D, Azam S, et al I. Acute dilated cardiomyopathy in the setting of catastrophic antiphospholipid syndrome and thrombotic microangiopathy: A case series and review. EJHaem 2020;1:44-50.
[43] Schultz M, Wimberly K, Guglin M. Systemic lupus and catastrophic antiphospholipid syndrome manifesting as cardiogenic shock. Lupus 2019;28:1350-1353.
[44] Tulai IM, Penciu OM, Raut R, Rudinskaya A. Catastrophic Antiphospholipid Syndrome Presenting as Congestive Heart Failure in a Patient with Thrombotic Microangiopathy. Tex Heart Inst J 2019;46:48-52.
[45] Rosenbaum AN, Anavekar NS, Ernste FC, et al. A case of catastrophic antiphospholipid syndrome: first report with advanced cardiac imaging using MRI. Lupus 2015;24:1338-41.
[46] Plastiras SC, Tzelepis GE, Kelekis NL, Vlachoyiannopoulos PG. Catastrophic antiphospholipid syndrome with heart involvement: diagnostic utility of the cardiac MRI. Int J Cardiol 2007;116:e29-31.

[47] Alhassan E, Otaishan D, Aljohani S, Almubarak M. Massive Right Ventricular Thrombus Secondary to Catastrophic Antiphospholipid Syndrome. J Clin Rheumatol 2021;27:e77-e78.
[48] Waisayarat J, Plumworasawat S, Vilaiyuk S, Sirachainan N. Intracardiac thrombus in a patient with catastrophic antiphospholipid syndrome: an autopsy case report and review of the literature. Vasc Health Risk Manag 2019;15:253-258.
[49] Akdime F, Voiriot G, Lalevée S, et al. Simultaneous Left and Right Ventricular Thrombi Caused by Catastrophic Antiphospholipid Syndrome. Am J Respir Crit Care Med 2019;200:e147-e149.
[50] González-Pacheco H, Eid-Lidt G, Piña-Reyna Y, et al. Acute left main coronary artery thrombosis as the first manifestation of systemic lupus erythematosus and catastrophic antiphospholipid syndrome. Am J Emerg Med 2014;32:197.e3-5.
[51] Gologorsky E, Andrews DM, Gologorsky A, et al. Devastating intracardiac and aortic thrombosis: a case report of apparent catastrophic antiphospholipid syndrome during liver transplantation. J Clin Anesth 2011;23:398-402.
[52] Cranley J, Krishnan U, Tweed K, Duehmke RM. Catastrophic antiphospholipid syndrome causing ST-segment elevation myocardial infarction with non-obstructive coronary arteries. BMJ Case Rep 2019;12:bcr-2018-225495.
[53] Sahashi Y, Serge Yanagimoto T, Endo S, Ushikoshi H, Okura H. Sudden Cardiac Arrest as the First Manifestation in a Patient with Catastrophic Antiphospholipid Syndrome. Intern Med. 2020;59:1457-1460.
[54] Gartshteyn Y, Bhave N, Joseph MS, Askanase A, Bernstein EJ. Inflammatory and thrombotic valvulopathies in autoimmune disease. Heart 2023;109:583-588.
[55] Coletto LA, Gerosa M, Valentini M, et al. Myocardial involvement in anti-phospholipid syndrome: Beyond acute myocardial infarction. Autoimmun Rev. 2022;21(3):102990.
[56] Pons I, Louro J, Sitges M, Vidal B, Cervera R, Espinosa G. Heart Valve Involvement in Patients with Antiphospholipid Syndrome: A Long-Term Follow-Up Study of a Single Centre. J Clin Med. 2023;20;12:2996.
[57] Pardos-Gea, J.; Ordi-Ros, J.; Avegliano, G.; Cortés-Hernández, J.; Balada, E.; Evangelista, A.; Vilardell, M. Echocardiography at diagnosis of antiphospholipid syndrome provides prognostic information on valvular disease evolution and identifies two subtypes of patients. Lupus 2010;19:575–582.
[58] Krause, I.; Lev, S.; Fraser, A.; Blank, M.; Lorber, M.; Stojanovich, L.; Rovensky, J.; Chapman, J.; Shoenfeld, Y. Close association between valvar heart disease and central nervous system manifestations in the antiphospholipid syndrome. Ann. Rheum. Dis 2005;64:1490–1493.
[59] Tripodi A. Diagnostic Challenges on the Laboratory Detection of Lupus Anticoagulant. Biomedicines. 2021;9(7):844.