Granuloma Annulare: a Case-control Study of Possible Associated Diseases

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ABSTRACT

Introduction: Granuloma annulare (GA) has been reported as associated with multiple diseases, mainly diabetes mellitus (DM), thyroid diseases, and dyslipidemia. However, the high prevalence of some of these illnesses makes it difficult to assess whether the association is real or fortuitous.

Objectives: Our objective was to analyze the clinical features of GA patients and the possible associations.

Methods: This is a retrospective observational study of 225 patients with biopsy-proven GA diagnosed between 2009 and 2019 in a referral university hospital in Barcelona, Spain. Clinical charts were reviewed to obtain clinical data. As a control group we used a random list of 225 patients diagnosed in the hospital traumatology department in the same period, matched by age and sex.

Results: Diabetes was diagnosed in 40 GA patients (18%) (34 in the control group, 15%) and hypothyroidism in 33 (15%) (22 in the control group 9.8%); the differences were not significant. We also did not detect any association with uveitis, sarcoidosis, necrobiosis lipoidica, Sweet syndrome, HIV infection, hepatitis B, or hematological malignancies. We only detected a possible association with hepatitis C (6 GA patients, 2.7%, versus 0 controls, P = 0.03), and hypercholesterolemia (108 GA patients, 48%, versus 79 controls, 35%, P = 0.007).

Conclusions: The possible pathogenic explanations for the association with hepatitis C and hypercholesterolemia seem unlikely. We consider that the association of GA with other diseases, including hypercholesterolemia and hepatitis C, is doubtful and that it there is no justification rule out possible associated diseases in patients with GA.

Introduction

Granuloma annulare (GA) is a disease of the skin and subcutaneous tissue of unknown etiology characterized by annular plaques, papules, or nodules containing foci of altered collagen surrounded by histiocytes and lymphocytes. It is a relatively frequent entity with a benign clinical course that in most cases does not require treatment [1,2]. It has been reported as associated with multiple diseases, mainly diabetes mellitus (DM), thyroid diseases, and dyslipidemia. However, the high frequency of some of these illnesses in the general population makes it difficult to assess whether the association is real or fortuitous [1,3]. Although there are multiple studies on the subject, to date no adequately controlled studies have been performed [1].

Objectives

Our objective was to review a series of patients with GA diagnosed histologically in the last 10 years in our hospital in order to analyse their clinical features and the possible association with other diseases.

Methods

We carried out a retrospective observational study of a series of 225 patients clinically and histologically diagnosed with GA between 2009 and 2019 at Bellvitge Hospital in Barcelona. This is a tertiary referral university hospital that provides healthcare to a population of approximately 1 million people. Cases registered as GA in the database of the pathology department were reviewed. The diagnostic criteria were the presence of palisaded granulomas with mucin deposition inside the granuloma.

Cases with lesions limited to the limbs or trunk were classified as localized GA, while those with lesions on the trunk and extremities (upper, lower, or both) were considered generalized GA [4]. Cases with epidermal perforation on biopsy were diagnosed with perforating GA, and the cases with lesions limited to the hypodermis were classified as subcutaneous GA. Finally, cases with large erythematous or brownish smooth-surface macules on the trunk and extremities without induration and with a histological pattern of interstitial GA were classified as patch GA [5]. The medical records of the patients were retrospectively reviewed to obtain the following data: race, sex, age of the patients at the time of diagnosis, date of diagnosis, evolution time of the lesions, number of lesions, location, clinical form of GA (localized, generalized, subcutaneous, perforating, and patch-type), duration of the lesions, presence of DM, hypercholesterolemia, thyroid diseases, uveitis, HIV, hepatitis B, hepatitis C,

hematological neoplasms, sarcoidosis, Sweet syndrome, and association with drug treatments. The treatments carried out and the follow-up time of the patients were also recorded.

Control Group

For a control group, a random list of patients diagnosed in our hospital traumatology department between 2009 and 2019, was used. For each case, a control of the same age and sex was randomly taken. For case and control, the clinical history of the patients in the public health system was accessed to record whether they were diagnosed with the above cited entities by their primary care physician before or during the year of the diagnosis of GA or of the visit to traumatology. All controls were Caucasian except for 1 male and 3 females of South American descent.

Statistical Analysis

Data were explored with the SPSS 17.0 statistical package for Windows. The proportions of cases with the possible associated diseases in the group of patients with GA and in the control group were compared using Fisher exact test. The possible relationships between the different variables analyzed were also investigated. Categorical variables were compared using Fisher exact test. Continuous variables were compared using Student t test when the normality of the data distribution was confirmed. Otherwise, the Mann-Whitney U test was performed. Statistical significance was established at a value of $P < 0.05$.

Results

These were 225 patients, 155 women (69%) and 70 men (31%), aged between 4 and 91 years (mean age 54.91 years, standard deviation [SD] 16.296). At the time of diagnosis, 155 patients were older than 50 years (69%). All patients with GA were Caucasian except for 2 women of South American descent. GA lesions involved the upper extremities in 150 patients (hands 69, elbows 64, rest of the upper extremities 78), the lower extremities in 92 (feet 15, knees 22, rest of the lower extremities 78), the trunk in 82 (anterior part of the trunk 70, posterior part 40), and the head and neck region in 25 (19 neck, 6 face). Classic localized GA was the most frequent form of GA (124 cases, 55%) followed by generalized GA (72 cases, 32%), patch-type GA (35 cases, 16%, some of them generalized), subcutaneous GA (6 cases 2.7%) and perforating GA (4, 1.8%). Among the 191 cases in which the extent of the lesions could be assessed, 117 had fewer than 10 lesions and 74 had more than 10 lesions. The time of evolution of the lesions at diagnosis was 11.74 months, SD 19.284. The duration of the lesions until healing or the last follow-up was established in 112 cases,

ranging between 1 and 240 months (mean 31.46 months, SD 39.921). In 68 of these 112 cases, the lesions persisted for less than 2 years (61%). In 23 patients the lesions were recurrent. The follow-up time of the patients ranged between 1 and 120 months, with a mean follow-up of 21.83 months, SD 27.851. The prescribed treatments were: no treatment in 46 patients, topical corticosteroids in 163, systemic corticosteroids in 30, topical tacrolimus in 22, antimalarials in 14, intralesional corticosteroid infiltrations in 8, pentoxifylline in 8, dapsone in 2, tetracyclines in 2, and isotretinoin in 1. Twenty patients received 3 or more treatments.

Table 1 shows the clinical features of the lesions according to the sex of the patients. Table 2 shows the diseases detected in the cases and in the controls.

In the analysis of the possible relationships between the variables analyzed, the following relationships were significant: male patients more frequently had hand lesions than female patients (P = 0.017); female patients had lower limb lesions more frequently than male patients (P = 0.002); patients with patch GA more frequently had lesions on the trunk (P = 0.020) and lower limbs (P = 0.013) than the rest of the patients; and finally, in a higher proportion of patients with less than 10 lesions, the lesions involved the upper extremities compared to the rest of the patients (P = 0.015).

Conclusions

Although the incidence of GA in the population is unknown, it is one of the most frequent chronic dermatological diseases. GA has been estimated to represent approximately 0.1–0.4% of dermatology outpatient visits in the United Kingdom [6] and 0.22-0.27% in the United States of America [7]. In our hospital we have not quantified the number of visits due to GA but the histological diagnosis of GA represents 0.97% of the skin biopsies.

According to the literature, GA occurs more frequently in the first 3 to 5 decades of life, with a ratio of women to men of around 1-2:1 [2]. In some series the percentage of women is higher, up to 85% [7], being 69% in our series (female / male ratio of 2.21 / 1). Regarding age, we had a higher mean age than in other series (55 years, with 155 cases over 50 years), probably due to the lack of pediatrics department in our hospital.

It is known that GA lesions are usually located in the extremities, especially the back of the hands and feet [2]. In our series, the upper extremities were affected in 150 patients (67%) and the lower extremities in 92 (41%), but the trunk was also frequently affected (82 cases, 36%). There are five common clinical variants of GA (localized, generalized, patch-type, subcutaneous, and perforating). According to the

Table 1. Clinical features according to the sex of the patients.

	Female 155 (69%)	Male 70 (31%)	
Age, years	54.62 SD 16.041	55.54 SD 16.948	
Evolution at diagnosis (months) 11.74 SD 19.284	12.56 SD 21.874	9.87 SD 11.236	
Total duration (months) 31.36 SD 39.921	32.92 SD 44.453	27.94 SD 26.330	
Upper limbs. N 150 (67%)	106/155 (68%)	44/70 (63%)	p = 0.017
Hands 69	40	29	p = 0.006
Elbows 64	53	11	
Rest 78	60	18	
Lower limbs, N 92 (41%)	75/155 (48%)	17/70 (24%)	p = 0.002
Feet 15	12	3	p < 0.001
Knees 22	18	4	
Rest 78	67	11	
Trunk, N 82 (36%)	59/155 (38%)	23/70 (33%)	
Anterior 70	49	21	
Posterior 40	29	11	
Head and neck, N 25 (11%)	14/155 (9%)	11/70 (16%)	
Neck 19	10	9	
Face 6	4	2	
Generalized, N 72 (32%)	54 (35%)	18 (26%)	
Patch, N 35 (16%)	26 (17%)	9 (13%)	
Subcutaneous, N 6 (2.7%)	2 (1.3%)	4 (5.7%)	
Perforating, N 4 (1.8%)	2 (1.3%)	2 (2.9%)	
>10 lesions, N 74/191 (39%)	55/132 (42%)	19/59 (32%)	

SD = standard deviation.

Table 2. Diseases detected in cases and in controls.

	225 GA cases	225 controls	
Age	54.91 SD 16.296	55.12 SD 16.321	
Sex (female/male), N	155/70	155/70	
DM, N 1 2	40 (18%) 3 37	34 (15%) 2 32	
Hypothyroidism, N	33 (15%)	22 (9.8%)	
Hypercholesterolemia, N	108 (48%)	79 (35%)	P = 0.007
Hematologic neoplasms, N	4 (1.8%)	1 (0.4%)	
HIV, N	1 (0.4%)	0	
Hepatitis B, N	3 (1.3%)	1 (0.4%)	
Hepatitis C, N	6 (2.7%)	0	P = 0.030
Sarcoidosis, N	1 (0.4%)	0	
Necrobiosis lipoidica, N	1 (0.4%)	0	
Uveitis, N	0	0	
Sweet syndrome, N	0	0	

DM = diabetes mellitus; SD = standard deviation.

literature, the most common is localized GA, accounting for approximately 75% of GA cases. Generalized GA represents 10-15% of cases [4,6] and is observed predominantly in adults. It is defined as the presence of lesions on the trunk and extremities (upper or lower or both) [4]. Patch-type GA is defined by the development of large erythematous or brownish patches with a smooth surface on the trunk and extremities with a histological pattern of interstitial GA [5]. Perforating GA, characterized by umbilicated papules with a central crust or a hyperkeratotic nucleus, and subcutaneous GA are less frequent [1,2]. In our series we had a lower proportion of localized GA (55%) and a higher proportion of generalized GA (32%) and patch-type GA (16%). This may be explained by the fact that our study only included histologically confirmed cases diagnosed in a referral hospital that receives the most doubtful, extensive, or persistent cases. This may also explain the high proportion of trunk lesions in our series.

In previous studies, GA lesions resolved within 2 years in 50% of cases [8]. In our patients, the lesions resolved within 2 years in 68 of 112 cases in which the duration of the lesions could be determined (61%). Although in our patients GA lesions may have been extensive and persisted for long time, the only complication observed in them was secondary elastolysis in some cases of generalized GA.

Various diseases have been considered as being possibly associated with GA, including metabolic, endocrinological, autoimmune, granulomatous, infectious, and hematological diseases. Although a possible association with malignant neoplasms has also been proposed based on isolated cases and short series, a recent case-control study with a series of 60 cases of generalized GA did not detect significant differences with the control group (19% in the group with GA and 9.33% in the control group) [9]. For this reason, we consider it unlikely that GA is associated with malignant solid neoplasms and we did not investigate this possibility it in the present study.

Diabetes mellitus (DM) is the disease most frequently analyzed as possibly being associated with GA. Some articles suggest that there is a putative association [3,10-12], especially with generalized GA [4], while other articles reject this [13-15]. The association with DM has been attributed to microvascular dysfunction induced by diabetes. In addition, as diabetes is associated with elevated inflammatory cytokines as well as T-cell and macrophage activation, it has been suggested that diabetes may act as risk factor for GA through dysregulated T-cell activity. In the present study, 40 of the 225 patients with GA (18%) were diabetic at diagnosis or had a diagnosis of DM in the subsequent 12 months, compared to 34 in the control group (15%), a difference that was not statistically significant. Among the 72 cases of generalized GA, the incidence of DM was similar (13/72, 18%) and the differences were therefore not significant either. There are also several studies that suggest a possible association with thyroid diseases, especially hypothyroidism [7,16]. As GA is considered an autoimmune disease, it has been suggested that the association of GA with autoimmune thyroidal diseases may be based on a common immunogenetic predisposition. In our study, 33 of our patients with GA (15%) were diagnosed with hypothyroidism compared to 22 in the control group (9.8%) and the difference was also not significant. Other diseases that have been reported

with some frequency as being associated with GA are uveitis [17,18], sarcoidosis [19,20], necrobiosis lipoidica [21], and Sweet syndrome [22]. In the present study we did not detect a significant association with any of them. Regarding infections, possible associations with HIV infection, hepatitis B, and hepatitis C have been suggested [3]. We did not detect an association with HIV or hepatitis B, but 6 of our GA patients had positive serology for hepatitis C (2.7%) compared to none of the controls. Although the number of cases is limited, the differences were significant (P = 0.03). As a possible pathogenesis, it has been suggested that infection by hepatitis C virus may generate a cell-mediated immune response that induces the formation of granulomas, since the presence of epithelioid granulomas in the liver has been detected in 10% of patients with HCV-related cirrhosis [23]. In addition, in some patients with generalized GA and hepatitis C, resolution of cutaneous lesions has been reported after hepatitis treatment [23,24]. Our data suggest that although in some patients infection by hepatitis C virus may induce GA, this situation is extremely rare, and in most cases GA is not related to hepatitis C virus infection.

The most noteworthy of our results is that we detected a significantly higher incidence of hypercholesterolemia among patients with GA than among controls, 108 cases (48%) versus 79 cases (35%) (P = 0.007). The association of GA with dyslipidemia was detected in a previous study in which 80% of 140 patients with GA had dyslipidemia compared with 52% of the controls (P < 0.001) [25]. This survey also detected a significant association with the extent of the lesions and a higher prevalence of dyslipidemia in generalized GA. In contrast, in our series the comparison of the incidence of hypercholesterolemia between generalized and localized GA did not reveal significant differences. The pathogenic mechanisms that might explain the relationship between GA and hypercholesterolemia are unclear. Observations that support an association between GA and dyslipidemia include the presence of lipid droplets in a considerable proportion of GA biopsies [21,26], and the histological similarity of GA to eruptive xanthoma [27,28]. It has also been suggested that the association of GA with dyslipidemia may be due to inflammation caused by the granulomatous disease itself, since chronic inflammation in diseases with cytokine patterns similar to GA, such as lichen planus and psoriasis, can trigger dyslipidemia [29-31]. On the other hand, the presence of microangiopathy in GA similar to that observed in necrobiosis lipoidica suggests that the granulomatous process may be secondary to microvascular dysfunction as a result of hypercholesterolemia [32,33]. Healing of GA lesions after dyslipidemia treatment also lends supports to a pathogenic relationship between the two entities [34]. However, these putative explanations are not widely accepted and some seem unlikely. The high incidence of hypercholesterolemia in the general population and the lack of uniformity in the diagnostic criteria for hypercholesterolemia make these results difficult to assess. For this reason, despite the significant differences in the proportion of patients diagnosed with hypercholesterolemia among those with GA compared to the control group in the present study, we consider a pathogenic relationship between both entities to be unlikely.

One limitation of our study is that it is a retrospective survey and some clinical data of the patients are not included in the medical records. Another limitation is that these are cases diagnosed by biopsy in a referral hospital without pediatrics department, so generalized cases may be overestimated and the adult population may be overrepresented. As for the case-control study, the high frequency of some diseases in the general population makes it difficult to investigate a true relationship with GA.

In summary, our study did not detect an association between GA and pathologies such as DM and hypothyroidism. We only detected a significantly higher proportion of patients with hypercholesterolemia and hepatitis C than in the control group. However, the possible pathogenic explanations for this association seem unlikely. We feel that association with other diseases, including hypercholesterolemia and hepatitis C, is doubtful and that it is not justified to systematically rule out the existence of possible associated diseases in patients with GA.

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