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Research Article

Follow-up of patients with sarcoidosis in an internal medicine unit from a hospital in Asturias, Spain. Analysis of extrapulmonary manifestations

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Objectives

Sarcoidosis is a multisystem disease of unknown origin that is characterized by non-caseating epithelioid granuloma formation within various organs, mainly the lungs [1].

The objective of this study is the analysis of sarcoidosis patients affected by pulmonary manifestation alone or extrapulmonary expression.

Methods

A retrospective review of patients diagnosed with sarcoidosis at Central University Hospital of Asturias (Oviedo, Spain), between July 1977 and January 2021. Diagnosis of sarcoidosis is based on the histopathological diagnosis and the organic affectations including clinical and radiological presentation. But the diagnosis of sarcoidosis was accepted without histological confirmation in other circumstances: Löfgren síndrome; and asymptomatic finding of typical hiliar lymphadenopatic.

Regarding organic involvement, the following have been studied: pulmonary, cutaneous, ocular, hepatic, splenic, salivary glands, otolaryngological, joints, bone, muscular, renal, phosphocalcium metabolism, neurological, cardiological and bone marrow.

In addition, the following biochemical changes were evaluated: calcium levels expressed in millimoles per liter (mmol/L), serum angiotensin-converting enzyme (SACE) in Units per liter (U/L).

Scadding JG staging system was used, as well as other radiological imaging studies such as computed tomography (CT) and positron emission tomography (PET) scan, especially to evaluate extrapulmonary involvement.

The data was recorded and analyzed using the statistical software R in version 4.1.2. The qualitative variables were summarized by their frequency distribution and the quantitative variables by the mean and standard deviation or median and interquartile range. Comparisons of qualitative variables: chi-square test. For quantitative: the U Mann-Whitney test and T-student.

A p - value < 0.05 was considered statistically significant and as a measure of association, the Odd ratio (OR), is considered statistically significant if its confidence interval (CI) does not include [1]. Those variables that reached statistical significance in the univariate analysis were introduced in the multivariate analysis.

The research protocol has been approved by the Ethics and Clinical Research Committee of the Central University Hospital of Asturias (Oviedo, Spain).

Results

One hundred and six patients were diagnosed with sarcoidosis over forty-four years at Central University Hospital of Asturias (Oviedo, Spain), sixty-one were women

(57.6%) and forty-five (42.4%) were men. Sex ratio (F/M: 1.35). The median age at diagnosis was 49.2 years (range: 38.2 - 60.1).

Table 1 shows organic affectation.

Extrapulmonary involvement was found in 84 patients (79.2%) and located exclusively (thoracic) in 22 patients (20.8%).

The chronic form of the disease, considered the presence of the disease with more than 5 years of evolution since its diagnosis, has been observed in 78 patients (73.6%). Being more noticeable in women OR 3.46 (1.36- 9.38) with *p* - value = 0.01.

In relation to the radiological classification by pulmonary involvement, no differences have been found between males and females (46.7% and 41%) respectively, $p = 0.692$.

We have also studied the relationship between radiological stages and calcium levels, in stages I, II and III, calcium levels have been normal, but all patients in stage IV presented hypercalcemia, $p < 0.001$, OR: 2.71 (1.35 - 4.07).

Serum values for calcium were similar in males and females (2.4 mmol/L RIQ 2.3 - 2.5), while (SACE) values in males were slightly higher (81.5 U/L RIQ 58 - 101) than in females (77 U/L RIQ 53 - 91), but without reaching statistical significance.

When comparing clinical and analytical variables: (age, sex, extrathoracic adenopathies, time of evolution, respiratory symptoms, general symptoms, serum ACE (SACE) levels, calcium and pulmonary radiological classification), between systemic and localized sarcoidosis, no statistically significant differences have been found in general, except in systemic involvement with: higher serum SACE levels with OR 1.02 (1.0 - 1.04) with a value of $p = 0.04$, a greater presence of extrathoracic adenopathies with a value of $p = 0.031$, splenomegaly and otolaryngological area involvement with values of $p = 0.028$ and 0.034 respectively.

Discussion

The prevalence of extrapulmonary sarcoidosis varies among populations. We found that 79.2% of patients with pulmonary sarcoidosis had extrapulmonary involvement. In previously conducted studies 30% - 50% of patients showed extrapulmonary disease localizations or SF [2,3]. We think the higher incidence in our study is because the patients were sent to the Autoimmune Diseases Unit. Patients with predominant pulmonary location are studied by the Pneumology Unit. The most common sites found globally in our study were: cutaneous, extrathoracic lymph nodes, and ocular involvement, which agrees with other series [3,4]. Skin lesions show fundamentally non-specific forms, without granulomatous findings in a biopsy, represented by erythema nodosum, as it happens in other Spanish series [4]. A Case-Control Etiologic Study of Sarcoidosis (ACCESS) showed that out of 736 patients with sarcoidosis, 95% had pulmonary involvement and that 368 of these 736 (50%) had concomitant extrapulmonary involvement [5]. The extrapulmonary disease may manifest before, concurrent with, or after the development of pulmonary disease depending on the localization of symptoms [6]. In another study out of 638 patients with biopsy-proven sarcoidosis, 258 (40.5%) had extrapulmonary involvement [3].

ACCESS demonstrated that Caucasians more frequently

Table 1: Distribution of the 106 patients diagnosed with sarcoidosis according to sex and location of the disease.

Organic affectation	Gender						[1]*p* value
	Female (*n* = 61)		Male (*n* = 45)		Total (*n* = 106)		
	n	57.6%	*n*	42.4%	*n*	100%	
Chest Radiograph Stage							
Stage 0	12	(19.7%)	3	(6.7%)	15	(14.2%)	
Stage 1	24	(39.3%)	21	(46.7%)	45	(42.5%)	
Stage 2	14	(23.0%)	15	(33.3%)	29	(27.4%)	0.249
Stage 3	9	(14.8%)	4	(8.9%)	13	(12.3%)	
Stage 4	2	(3.2%)	2	(4.4%)	4	(3.7%)	
Cutaneus	31	(51.7%)	12	(26.7%)	43	(41.0%)	0.0157
Extrathoracic Lymph nodes	17	(28.3%)	13	(29.5%)	30	(28.8%)	1.0
Ocular	13	(21.7%)	12	(26.7%)	25	(23.8%)	0.645
Hepatic	12	(20.0%)	7	(15.6%)	19	(18.1%)	0.617
Spleen	6	(10.2%)	6	(13.3%)	12	(11.5%)	0.759
Salivary glands	3	(5.0%)	4	(8.89%)	7	(6.7%)	0.458
Otolaryngological	4	(6.67%)	0	(0.0%)	4	(3.8%)	0.133
Joint/bone	4	(6.7%)	3	(6.7%)	7	(6.7%)	1
Muscular	1	(1.67%)	1	(2.22%)	2	(1.9%)	1
Renal	3	(5.0%)	8	(17.8%)	11	(10.5%)	0.0517
Neurological	6	(10.0%)	4	(8.9%)	10	(9.5%)	1
Cardiological	1	(1.7%)	1	(2.2%)	2	(1.9%)	1
Bone marrow	3	(5.0%)	4	(8.9%)	7	(6.7%)	0.458
Calcium metabolism	6	(10.0%)	10	(22.2%)	16	(15.2%)	0.104

[1]The *p* - value associated with a chi-square proof of dependence.

had sarcoidosis-related calcium metabolism disorders [5] and that uveitis is fairly common in black and Asian patients (10% - 30% prevalence) [1].

As we have observed, extrapulmonary sarcoidosis may be most frequent in females [7], they also have a higher prevalence of skin involvement and uveitis [7].

We have found, as in other studies, that patients with pulmonary and extrapulmonary involvement (systemic involvement), have higher levels of SACE than patients with isolated pulmonary sarcoidosis [3]. SACE is produced in the epithelioid cell of the sarcoid granuloma, also SACE level had been correlated with extrapulmonary organ involvement and overall disease activity [8,9].

Since the 1930´s it has been known that patients with sarcoidosis can develop hypercalcemia, which can affect their general condition and damage the internal kidney, leading to renal insufficiency. The mechanism by which patients may have an increased risk of developing hypercalcemia is not fully understood. Studies have reported an increased risk for patients of White European ancestry, male sex and over 40 years of age. The average duration between sarcoidosis diagnosis and detection of hypercalcemia was 1.39 years, when it occurs it´s considered a progressive form of the disease [10].

Our work had several limitations like retrospective design and the sending of patients to an Autoimmune Diseases Unit, which means that these patients have less respiratory involvement. Our results suggest that the extrapulmonary involvement of sarcoidosis is frequent in our environment. The presentation profile is that of a 40-year-old woman with the presence of extrathoracic adenopathies, splenomegaly and otolaryngological involvement.

References

1. Valeyre D, Prasse A, Nunes H, Uzunhan Y, Brillet PY, Müller-Quernheim J. Sarcoidosis. Lancet. 2014 Mar 29;383(9923):1155-67. doi: 10.1016/S0140-6736(13)60680-7. Epub 2013 Oct 1. PMID: 24090799.
2. Rao DA, Dellaripa PF. Extrapulmonary manifestations of sarcoidosis. Rheum Dis Clin North Am. 2013 May;39(2):277-97. doi: 10.1016/j.rdc.2013.02.007. Epub 2013 Mar 13. PMID: 23597964; PMCID: PMC3756667.
3. Li CW, Tao RJ, Zou DF, Li MH, Xu X, Cao WJ. Pulmonary sarcoidosis with and without extrapulmonary involvement: a cross-sectional and observational study in China. BMJ Open. 2018 Feb 16;8(2):e018865. doi: 10.1136/bmjopen-2017-018865. PMID: 29453299; PMCID: PMC5829779.
4. Mañá J, Rubio-Rivas M, Villalba N, Marcoval J, Iriarte A, Molina-Molina M, Llatjos R, García O, Martínez-Yélamos S, Vicens-Zygmunt V, Gámez C, Pujol R, Corbella X. Multidisciplinary approach and long-term follow-up in a series of 640 consecutive patients with sarcoidosis: Cohort study of a 40-year clinical experience at a tertiary referral center in Barcelona, Spain. Medicine (Baltimore). 2017 Jul;96(29):e7595. doi: 10.1097/MD.0000000000007595. PMID: 28723801; PMCID: PMC5521941.
5. Baughman RP, Teirstein AS, Judson MA, Rossman MD, Yeager H Jr, Bresnitz EA, DePalo L, Hunninghake G, Iannuzzi MC, Johns CJ, McLennan G, Moller DR, Newman LS, Rabin DL, Rose C, Rybicki B, Weinberger SE, Terrin ML, Knatterud GL, Cherniak R; Case Control Etiologic Study of Sarcoidosis (ACCESS) research group. Clinical characteristics of patients in a case control study of sarcoidosis. Am J Respir Crit Care Med. 2001 Nov 15;164(10 Pt 1):1885-9. doi: 10.1164/ajrccm.164.10.2104046. PMID: 11734441.
6. Rao DA, Dellaripa PF. Extrapulmonary manifestations of sarcoidosis. Rheum Dis Clin North Am. 2013 May;39(2):277-97. doi: 10.1016/j.rdc.2013.02.007. Epub 2013 Mar 13. PMID: 23597964; PMCID: PMC3756667.
7. Jayakrishnan B, Al-Busaidi N, Al-Mubaihsi S, Al-Rawas OA. Sarcoidosis in the Middle East. Ann Thorac Med. 2019 Apr-Jun;14(2):106-115. doi: 10.4103/atm.ATM_227_18. PMID: 31007761; PMCID: PMC6467024.
8. Prasse A. The Diagnosis, Differential Diagnosis, and Treatment of Sarcoidosis. Dtsch Arztebl Int. 2016 Aug 22;113(33-34):565-74. doi: 10.3238/arztebl.2016.0565. PMID: 27598883; PMCID: PMC5015588.
9. Yasar Z, Özgül MA, Cetinkaya E, Kargi A, Gül Ş, Talay F, Tanriverdi E, Dincer HE. Angiotensin-converting Enzyme as a Predictor of Extrathoracic Involvement of Sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2016 Jan 18;32(4):318-24. PMID: 26847099.
10. Werner J, Rivera N, Grunewald J, Eklund A, Iseda T, Darlington P, Kullberg S. HLA-DRB1 alleles associate with hypercalcemia in sarcoidosis. Respir Med. 2021 Oct;187:106537. doi: 10.1016/j.rmed.2021.106537. Epub 2021 Jul 22. PMID: 34325227.