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Sarcoidosis: A Single Hospital-Based Study in a 24-Year Period

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ABSTRACT

Background: Clinical presentation of sarcoidosis varies according to race and geographical area. We describe the clinical spectrum and outcome of sarcoidosis in Mexican patients compared with other populations. **Methods:** We reviewed the medical charts of 21 patients with sarcoidosis seen at a referral hospital in 1989-2012; organ involvement was assessed using the ACCESS instrument. We compared our results with the ACCESS and Latin American studies. We used descriptive statistics and reported odd ratios with 95% CI. **Results and Conclusion:** Fifty-two percent were women; median age was 31 years; median time to diagnosis, 5.5 months. Frequency of organ involvement was: constitutional symptoms 62%, lungs 66.6%, skin 42.8%, bone marrow 23.4%, lymph node 19%, liver 19%, and eye 19%. After one year of follow-up, 47.5% of patients were asymptomatic without treatment, 38% asymptomatic on treatment, and 14.2% symptomatic on treatment. In our patients, pulmonary involvement was lower (66.6 vs. 94.9%; p = 0.001) and cutaneous (42.8 vs.15.8%; p = 0.003) and bone marrow (23.4 vs. 4.7%; p = 0.001) were higher than in the ACCESS cohort. Data regarding Latin American populations was scarce. The clinical spectrum of sarcoidosis in our population differed from other studies, with a higher frequency of cutaneous sarcoidosis and less pulmonary involvement. (REV INVEST CLIN. 2015;67:33-8)
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INTRODUCTION

Sarcoidosis is a multisystem, inflammatory disorder of unknown etiology that affects individuals worldwide and is histologically characterized by non-caseation granulomas. The clinical presentation includes several manifestations, ranging from an asymptomatic or mild disease to a life-threatening condition[1].

Epidemiological studies among different ethnic groups have shown a substantial variation in the frequency, clinical characteristics, and severity of the disease[2,3].

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African Americans and northern European individuals have the highest rates of sarcoidosis, whereas it is uncommon in Japan, Spain, and Portugal[4-7]. In Latin America there are only a few studies, mainly case reports, on the clinical characteristics of sarcoidosis[8-13]. In Mexico the real frequency of this disease is unknown.

We evaluated a group of Mexican patients with sarcoidosis attending a single referral hospital to describe the clinical, laboratory and radiological findings, treatment, and clinical outcome and compare the clinical spectrum of the disease with that of the original ACCESS cohort (A Case-Control Etiologic Study of Sarcoidosis) and with other populations mainly from Latin America.

METHODS

This was a retrospective study of patients seen at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, a referral hospital in Mexico City, between January 1989 and December 2012. We included patients with a clinical presentation and histological findings of sarcoidosis, i.e., non-caseation granulomas with stains and culture negative for tuberculosis or other granulomatous infectious diseases. Clinical charts were reviewed according to a pre-established protocol. We collected demographic data, age at disease onset, clinical features, and laboratory and imaging findings. We also recorded the time of follow-up, corticosteroid or immunosuppressor treatment, and the clinical outcome. Symptoms including cough, dyspnea, chest pain, and fever were recorded as reported by the patients. Weight loss was considered as a ≥ 5% decrease in body weight in the preceding few weeks or months. Arthralgia was defined as persistent pain in any joint of ≥ 2-weeks´ duration without swelling or tenderness. Arthritis and uveitis were diagnosed by a rheumatologist or an ophthalmologist, respectively. Lymphopenia was considered when the lymphocyte count was < 1,500/µl. Serum aminotransferases were considered elevated if they were ≥ 1.5 times the normal values. Hypercalcemia was defined as a corrected serum calcium > 10.5 mg/dl and hyperglobulinemia when levels were > 3.5 g/dl. Erythrocyte sedimentation rate (ESR) was calculated and corrected for age and sex. Serum angiotensin-converting enzyme (SACE) was considered abnormal if the result exceeded the upper limit value.

Initial chest radiographs were staged according to the Scadding criteria[14]:

– Stage 0: normal chest

– Stage I: normal lung parenchyma plus bilateral and hilar lymphadenopathy

– Stage II: pulmonary infiltrates plus bilateral hilar lymphadenopathy. Stage III: pulmonary infiltrates without hilar lymphadenopathy

– Stage IV: pulmonary fibrosis.

Thoracic computed tomography (CT) scan findings were also recorded. Restrictive ventilatory dysfunction was defined as a forced vital capacity (FVC) < 80% of the predicted value, while obstructive ventilatory dysfunction was a forced expiratory volume in one second/forced vital capacity (VEF1/FVC) < 70%. Organ involvement was considered when the affected system met the criteria for "definite" or "probable" according to the ACCESS organ assessment instrument[15], validated by us.

We compared our results with the original cohort where the ACCESS instrument was described. The ACCESS cohort included 736 patients of diverse ethnicities (53.4% white, 44.2% African American, 2.4% other)[16]. We also compared our data with studies in other populations especially from Latin America[9-13].

Statistical analysis

We used descriptive statistics according to the distribution of the variables. Prevalence estimates were reported with 95% CI. Categorical variables were compared using either X^2 or Fisher's exact test when appropriate. We reported odd ratios (OR) with 95% CI. A two-tailed $p < 0.05$ was considered significant. All analyses were performed using the SPSS for Windows 20.0® (SPSS Inc).

RESULTS

We identified 21 patients with sarcoidosis during a 24-year period; 11 (52%) were women. Fifty-seven percent had a history of smoking, with a median of four packets per year (range 1-20). The median time of follow-up was 12 months (range 1-110 months), median age at onset was 31 years (range 18-72 years),

Table 1. Clinical and laboratory findings in Mexican patients with sarcoidosis

Clinical findings	n (%)
General symptoms	
– Fever	10 (48)
– Fatigue	8 (38)
– Weight loss	9 (43)
– Night sweats	8 (38)
Pulmonary symptoms	
– Dyspnea	10 (48)
– Cough	8 (38)
– Chest pain	8 (38)
Extrapulmonary manifestations	
– Arthralgia	11 (52)
– Hepatomegaly	6 (29)
– Peripheral lymphadenopathy	4 (19)
– Uveitis	4 (19)
– Arthritis	2 (9.5)
– Parotid enlargement	2 (9.5)
– Nasal congestion	2 (9.5)
– Dysphonia	1 (5)
– Sicca syndrome	1 (5)
– Neuropathic pain	1 (5)
– Facial palsy	1 (5)
Cutaneous manifestations	
– Erythema nodosum	8 (38)
– Subcutaneous nodules	8 (38)
– Plaques	2 (9.5)
– Maculopapular lesions	2 (9.5)
– Ulcers	1 (5)
Laboratory Findings, mean value	
– ACE	91 ± 56 UI/l
– ALT	131 ± 62 U/l
– AST	82 ± 50 U/l
– ESR	67 ± 11 mm/hour

ACE: angiotensin-converting enzyme; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ESR: erythrocyte sedimentation rate.

and median time between the initial symptoms and final diagnosis was 5.5 months (1-132 months). Clinical and laboratory features are presented in table 1. Constitutional symptoms including fever, weight loss, fatigue, and night sweats were present in 62%. The mean weight loss was 11.4 ± 6.0 kg. Pulmonary symptoms were present in 57% of patients and six subjects (29%) developed Löfgren´s syndrome. The most prevalent extrapulmonary features were arthralgia (52%), skin lesions (43%), and hepatomegaly (29%). The most frequent skin lesions were erythema nodosum (38%) and subcutaneous nodules (38%). Overall, three patients were asymptomatic.

The main laboratory findings were hyperglobulinemia (48%), lymphopenia (38%), hypercalcemia (5%), increased serum aminotransferases (29%), and increased ESR (29%). Of 14 patients (67%) with available serum ACE results, levels were increased in 10. The tuberculin skin test (TST) was positive only in one of 13 patients in whom the test was done. This patient, who developed a 15 mm skin induration, had a negative clinical and laboratory workflow for active tuberculosis.

Table 2. Imaging findings in Mexican patients with sarcoidosis

Imaging Finding	n (%)
Chest radiograph (n = 17)	
– Peri-hilar lymphadenopathy	4 (24)
– Nodular involvement	4 (24)
– Mediastinal enlargement	2 (12)
– Fibrosis	2 (12)
– Interstitial infiltration	1 (6)
– Normal	9 (53)
Chest CT (n = 20)	
– Mediastinal lymphadenopathy	20 (100)
– Nodular pattern	10 (50)
– Fibrosis	3 (15)
– Reticular infiltration	1 (5)
– Ground-glass opacities	1 (5)

Chest radiographs were available in 17 patients and were abnormal in eight (47%). According to the Scadding radiographic criteria, nine (53%) were at Stage 0, six patients (35%) in Stage I, and two (12%) in Stage IV. All the patients with normal chest radiographs (Stage 0) had thoracic CT abnormalities suggestive of sarcoidosis, such as mediastinal lymphadenopathy and nodular involvement (Table 2). In addition, Gallium 67 scintigraphy was done in two subjects (9.5%), in both of whom it was positive.

Pulmonary function tests were available in 18 patients (86%), showing restrictive ventilatory dysfunction pattern in five (28%) and obstructive dysfunction in one patient (5%). We identified 34 biopsies. The skin was the most frequently sampled organ (52%) followed by mediastinal lymph node (48%), lung (19%), peripheral lymph node (19%), liver (14%), pancreas (5%), and parotid gland (5%).

Five patients (24%) received antituberculosis therapy for a median time of seven months prior to the diagnosis of sarcoidosis. Seventeen patients (81%) received systemic corticosteroid therapy for a mean time of 12 ± 9.7 months; 43% also received immunosuppressor therapy (azathioprine 29%, methotrexate 14%, antimalarial treatment 5%, cyclophosphamide 5%). Four patients (19%) only required symptomatic treatment.

Table 3. Organ involvement in Mexican patients with sarcoidosis compared with the ACCESS cohort

Organ involvement	Our series (n = 21) n (%)	95% CI	ACCESS cohort (n = 736) n (%)	OR 95% CI	P value
Lung	14 (66.6)	43-85	699 (94.9)	0.10 (0.04-0.27)	0.001
Skin	9 (42.8)	22-66	117 (15.8)	3.96 (1.63-9.6)	0.003
Lymph node	4 (19)	5-42	112 (15.2)	–	0.54
Eye	4 (19)	5-42	87 (11.8)	–	0.30
Liver	4 (19)	5-42	85 (11.5)	–	0.29
Erythema nodosum	8 (38)	18-62	61 (8.2)	6.8 (2.7-17.06)	0.002
Spleen	0	0-16	49 (6.6)	–	038
Neurologic	0		34 (4.6)	–	0.26
Parotid/salivary	1 (4.7)	0-24	29 (4.7)	–	0.57
Bone marrow	5 (23.8)	8-47	29 (4.7)	7.6 (2.6-22.2)	0.001
Hypercalcemia	1 (4.7)	0-24	27 (3.6)	–	0.55
Ear/nose/throat	1 (4.7)	0-25	22 (2.9)	–	0.48
Heart	0	0-16	17 (2.3)	–	1
Kidney	0	0-16	5 (0.6)	–	1
Bone/joint	0	0-16	4 (0.5)	–	1
Muscle	0	0-16	3 (0.4)	–	1

OR: odd ratios.

At one year after diagnosis, 10 patients (47.5%) were asymptomatic and without treatment, eight (38%) were asymptomatic and on treatment, and three patients (14.2%) were symptomatic and on treatment. Two patients (9.5%) died, one from gastric carcinoma and the other from community acquired pneumonia.

Comparison with other populations

Table 3 shows the comparison of our results with those of the ACCESS cohort[16]. In our cohort, pulmonary involvement was statistically less frequent and cutaneous features, mainly erythema nodosum, were more common. We also found a higher prevalence of bone marrow involvement. Table 4 shows the distribution of different clinical features in Latin American populations (Argentina, Brazil, Costa Rica, Cuba)[9-12]. However, as these studies did not use the ACCESS definitions, we only provide a description of the data. We found a previous study done in Mexico, although it only evaluated patients with thoracopulmonary lesions[13].

DISCUSSION

Sarcoidosis is a multisystem disease that often presents insidiously and in which the diagnosis is not established by a single laboratory test. It is widely acknowledged that ethnicity probably modifies the prevalence and clinical presentation of the disease. The clinical presentation of sarcoidosis in Latin American and Mexican populations has been poorly described[8-13]. Here we described 21 Mexican patients with sarcoidosis and compared their clinical characteristics, diagnostic procedures, and clinical outcome with those of other populations.

According to the ACCESS study[16], the presentation of sarcoidosis may be affected by sex, race, and age. Regarding the age at disease onset, 67% of our patients were younger than 40 years, which is in agreement with previous studies[16,17]. Other Latin American patients had a similar age at disease presentation. In contrast, studies in Scandinavian[18], Japanese[8] and American[19] populations have found a large percentage of older patients, mainly women.

On the other hand, it has been reported that women with sarcoidosis are more likely to be ³ 40 years old, to have a higher frequency of erythema nodosum as well as eye and neurologic involvement, whereas men are more prone to develop hypercalcemia[16]. In our patients, due to an almost equal gender distribution, we could not find differences between men and women.

Table 4. Sarcoidosis in Latin America

Feature	Costa Rica (n = 15)	Argentina (n = 26)	Brazil (n = 100)	Cuba (n = 30)
Age in years, mean (range)	37 (17-55)	42.6 ± 12.7	60% < 40	28-89
Female, n (%)	8 (53)	14 (54)	56 (56)	14 (47)
Smoking history, n (%)	9 (60)	NR	35 (35)	NR
Dyspnea, n (%)	9 (60)	15 (58)	47 (47)	21 (7)
Fever, n (%)	2 (13)	5 (19)	2 (2)	NR
Weight loss, n (%)	2 (13)	6 (23)	8 (8)	NR
Peripheral lymph node, n(%)	NR	NR	21 (21)	16 (53)
Arthralgia/synovitis, n (%)	NR	NR	23 (23)	13 (14)
Skin involvement, n (%)	NR	NR	29 (29)	NR
Uveitis, n (%)	NR	NR	3 (10)	NR
Erythema nodosum, n (%)	NR	NR	4 (4)	NR
Asymptomatic, n (%)	1 (7)	4 (15)	10 (10)	NR
Prednisone treatment, n (%)	1 (7)	18 (69)	75 (75)	16 (62)
Immunosuppressive treatment, n (%)	0	3 (12)	2 (2)	NR
Scadding radiograph staging, n (%)				
– 0	0	6 (23)	15 (15)	
– I	12 (80)	2 (8)	19 (19)	
– II	2 (13)	8 (31)	43 (43)	NR
– III	1 (7)	7 (27)	20 (20)	
– IV	0	3 (12)	3 (3)	

NR= Not reported

Cigarette smoking has been described as a protective factor for sarcoidosis[20,21]. The ACCESS study reported that the variable "ever smoking" had a protective effect for sarcoidosis (OR: 0.65; 95% CI: 0.51-0.82)[20]. We observed that 57% of our subjects were cigarette smokers, a much higher proportion than that reported in Brazil[11] or Australia[22].

In our study the predominant organ involved was the lung, as it was in the ACCESS and the Medical University of South Carolina (MUSC) cohorts[16,23]. However, our prevalence was lower (65 vs. 95 and 89%, respectively). Our data are in agreement with other reports where up to 60% of patients with newly diagnosed sarcoidosis do not have pulmonary symptoms. In addition, the chest radiographic Scadding classification shows unequal grade frequencies worldwide[24]. Patients in Japan are more likely to have a Stage I disease compared with Europeans and Americans[16,23-25]. In our study, most patients had a Stage 0 (53%) and Stage I (35%) disease, which differs from the ACCESS (Stage 0 = 8.3 %)[16] and MUSC (Stage 0 = 33%) data[23]. In our patients the most common thoracic CT finding was mediastinal lymphadenopathy (100%) followed by nodules (50%), results similar to those reported in a Turkish population (92 and 49%, respectively)[26].

The presence of extrapulmonary clinical features in our cohort also showed differences when compared with the ACCESS cohort[16]. We observed a higher frequency of skin (specifically erythema nodosum) and bone marrow involvement, similar to patients in the MUSC cohort who also had a lower frequency of skin (26%) and bone marrow lesions (8%)[23]. Erythema nodosum is commonly seen in European patients although it is rare in Japanese and African American populations[6,16,23]. In the ACCESS cohort, African American patients were more likely to have skin lesions other than erythema nodosum and eye, liver, bone marrow, and extrathoracic lymph node involvement[16]. The frequency of this clinical manifestation, observed in 38% of our patients, was similar to that reported in Spain[27].

Some studies have suggested a low incidence of sarcoidosis in Latin America, probably related to genetic factors and environmental exposure to different antigens. We consider that this lower incidence may be biased due to unreported cases, and that prevailing endemic granulomatous diseases such as tuberculosis or chronic deep mycoses, which may clinically mimic sarcoidosis, confuse and delay the diagnosis. In our study, similar to what was reported in Brazil[28], diagnosis was delayed for almost six months and 20% of

our patients received tuberculosis treatment previous to a confirmation of sarcoidosis.

Excluding seriously ill or other immunosuppressed individuals, it appears that in 90% of the patients with sarcoidosis, the TST may be negative[29]. Moreover, a negative TST with a cutoff point of > 10 mm induration in a patient with a presumptive clinical diagnosis of sarcoidosis may reach a sensitivity of 100%[30]. Conversely, a positive TST in a patient with suspected sarcoidosis should be viewed with high diagnosis caution.

Finally, we observed that at one year of follow-up, the clinical course of sarcoidosis in our patients was towards an almost complete symptom remission. Similarly, data from the ACCESS cohort indicate that sarcoidosis tends to improve or remain stable over two years in the majority of patients[31].

In conclusion, despite the drawbacks of a retrospective study, the sample size, and the type of referral center, our results show a different clinical spectrum of sarcoidosis in the Mexican population. Our data showed early stages of pulmonary involvement and more cutaneous and bone marrow affliction, but also a more benign course. Although these results should not be generalized, they may reflect differences in the clinical course and management of sarcoidosis in our population that warrant further study. Ethnic and geographical differences may reflect diverse genetic susceptibility in this enigmatic disorder.

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