Original Investigation

Epidemiological characterization of patients with sarcoidosis in a high complexity hospital in southwestern Colombia

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ABSTRACT

Background/Objective: Epidemiological studies on sarcoidosis in Colombia are scarce, and although recent reports from the north of the country have been published, clinical-epidemiological associations are not clear. Our aim was to characterize patients with sarcoidosis diagnosed at Fundación Valle del Lili in Cali, Colombia.

Methods: A retrospective study of a series of sarcoidosis cases was conducted between 2011 and 2019. Demographic, clinical, laboratory, imaging, histopathological, and treatment variables were analyzed.

Results: A total of 34 patients with a diagnosis of sarcoidosis were found. The majority were women (n=25; 73%), and the mean age was 50 years. The main symptoms of onset were erythema nodosum (n=11; 33%), arthritis (n=10; 30%), and cough (n=9; 27%). In 64% of the cases, there was pulmonary involvement, with pulmonary nodules, mediastinal adenopathy, and interstitial lung disease found in 54%, 50%, and 36% of cases, respectively. In 85% of cases, there were extrapulmonary manifestations, mainly cutaneous (50%). Angiotensin-converting enzyme (ACE) was elevated in 62% of the cases in which it was measured (n=16; 47%). During the diagnostic process, 23 biopsies were performed, of which 95% showed granulomas with noncaseating necrosis. Most of the patients (76%) were controlled with prednisolone, at an average dose of 20 mg (7.5–50 mg) per day.

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**Introduction**

Sarcoidosis is an inflammatory multisystemic disease of unclear etiology; its typical histopathological feature is the existence of noncaseating epithelioid granulomas with mononuclear infiltrate and tissue microarchitecture destruction. Different hypotheses suggest that inside these granulomas lies a poorly degraded antigen surrounded by macrophages that differentiate until finally becoming epithelioid cells, which fuse to form multinucleated giant cells. As the name highlights, these granulomas do not present caseating necrosis, a phenomenon that is usually identified in tuberculous granulomas. Granulomas are generally composed of a mononuclear infiltrate of CD4+ T lymphocytes and macrophages, in addition to CD8+ T lymphocytes, regulatory T lymphocytes, fibroblasts, and B lymphocytes in the periphery.\(^2\)

The prevalence of sarcoidosis is close to 10 cases per 100,000 inhabitants, but the annual incidence is not known with certainty. It has a peak of onset typically between 50 and 69 years in women and between 40 and 59 years in men.\(^3,4\) It is more common in individuals with a genetic predisposition, mainly the HLA-B8, HLA-DRB1, and DQBQ alleles, and in individuals exposed to environmental triggers.\(^5,6\) Additionally, racial and geographic factors influence the prevalence and frequency of its clinical presentation; for example, black race is associated with a higher disease prevalence than Caucasian race, and within blacks it is more frequent in women than in men.\(^8\)

The clinical manifestations of sarcoidosis include a wide spectrum of presentations ranging from an asymptomatic state to ventilatory failure.\(^1\) The lungs are affected in more than 90% of cases. Pulmonary sarcoidosis is classified as a granulomatous interstitial pneumonia, has the highest

**Caracterización epidemiológica de pacientes con sarcoidosis en un hospital de alta complejidad en el sudoeste de Colombia**

**Resumen**

**Antecedentes/objetivo:** En Colombia son escasos los estudios epidemiológicos sobre la sarcoidosis; aunque recientemente se han publicado reportes del norte del país, son grupos muestrales pequeños, por lo que no quedan claras las asociaciones clinico-epidemiológicas. Nuestro objetivo fue caracterizar pacientes con sarcoidosis en la Fundación Valle del Lili, en Cali, Colombia.

**Métodos:** Se realizó un estudio retrospectivo de una serie de casos de sarcoidosis entre el 2011 y el 2019. Se analizaron variables demográficas, clínicas, de laboratorio, imagenológicas, histopatológicas y de tratamiento.

**Resultados:** Se encontraron 34 pacientes con diagnóstico de sarcoidosis, la mayoría fueron mujeres (n = 25; 73%), y la edad promedio fue 50 años. Los principales síntomas de inicio fueron eritema nudoso (n = 11; 33%), artritis (n = 10; 30%) y tos (n = 9; 27%). En el 64% de los casos hubo compromiso pulmonar, y se encontraron nódulos pulmonares, adenopatías mediastinales y enfermedad pulmonar intersticial en un 54, 50 y 36% de los casos, respectivamente. En el 85% de los casos hubo manifestaciones extrapulmonares, principalmente cutáneas (50%). Los niveles de enzima conversora de angiotensina estuvieron elevados en el 62% de los casos en los que fue medida (n = 16; 47%). Durante el proceso diagnóstico se realizaron 23 biopsias, de las cuales el 95% evidenció granulomas con necrosis no caseificante. La mayoría de los pacientes (76%) fueron controlados con prednisolona, a una dosis promedio de 20 mg (7,5-50 mg) por día.

**Conclusiones:** La sarcoidosis fue más frecuente en mujeres y mestizos. La presentación fue más temprana en hombres. La enzima conversora de angiotensina no se relacionó con compromiso extrapulmonar. Ni el perfil fósforo-calcio ni los anticuerpos antinucleares fueron útiles para establecer el diagnóstico.
incidence among chronic interstitial lung diseases, and can occur at any point of the disease. Patients may be diagnosed incidentally by chest imaging or may have a chronic presentation with nonspecific symptoms. These symptoms are usually hidden by other, more florid and specific extrapulmonary manifestations, such as erythema nodosum, which makes these patients take longer to be diagnosed, especially when pulmonary symptoms are presented as the only disease manifestation, because they are frequently confused with other more common diseases, such as asthma or chronic obstructive pulmonary syndrome. The disease can also affect other organs, such as the heart, liver, skin, eyes, musculoskeletal system, central nervous system, and/or upper airway. These facts, together with the absence of a definitive test to confirm the disease, makes sarcoidosis a diagnosis of exclusion, leading to a diagnostic success rate during the first attempt as low as 15%.

Although there are reviews about the epidemiological and clinical associations of sarcoidosis, especially in Europe, Asia, and North America, studies in the Latin American population are scarce. Specifically in Colombia, there are only two recent reports with small sample groups and a report on 51 patients published in 1977. For this reason, we wanted to describe our institutional experience with sarcoidosis at Valle del Lili Foundation University Hospital between January 2011 and July 2019.

Materials and methods

This is a retrospective observational case series study. Data were extracted from the electronic medical records of patients treated at Valle del Lili Clinical Foundation with a diagnosis of sarcoidosis between January 2011 and July 2019.

Demographic variables, symptoms at the beginning of the disease, affected organs and systems, and paraclinical tests at the time of diagnosis (including the serum level of angiotensin-converting enzyme, ACE) were analyzed. Additionally, computed tomography (CT) findings were evaluated, as were lung or other organ biopsies. Finally, treatments received.

Due to the retrospective and descriptive nature of the study, it was considered a minimal-risk study and was approved by the ethics and institutional research committee of Valle del Lili Foundation (protocol 1437). Statistical analysis was performed in STATA version 13®. The categorical variables are expressed as proportions and the quantitative variables as mean (standard deviation) or median (interquartile range). They were compared by the Mann–Whitney U test or two-sample t-test, according to the normality determined by the Shapiro–Wilk test.

Results

A total of 34 patients with a diagnosis of sarcoidosis were found. The majority were women (n = 25; 73.5%). The median age at diagnosis was 50 years, which was lower in men than in women (40 [32–49] vs. 50 [36–55] p = 0.0301). The most frequent ethnicity was mestizo (n = 28; 85%). The median duration between the onset of symptoms and diagnosis was 12 (6–24) months. The main manifestations at the beginning of the disease were erythema nodosum (n = 11; 33.3%), arthritis (n = 10; 30.3%), and cough (n = 9; 27.3%). Pulmonary involvement was present in 22 patients (64.7%), with cough, dyspnea, and chest pain in 50%, 13%, and 4% of patients, respectively. Additionally, in 85.3% of patients, extrapulmonary manifestations were evident, mainly cutaneous (50%), ophthalmological (32.3%), and musculoskeletal (32.3%). During the diagnostic process, chest CT was performed in 28 patients (82%), of whom seven did not have findings compatible with pulmonary sarcoidosis, so they were classified within the group of extrapulmonary sarcoidosis. Of the 22 patients with pulmonary sarcoidosis, pulmonary nodules, mediastinal adenopathy, and interstitial lung disease were found in 54%, 50%, and 36% of cases, respectively. The demographic, clinical, and imaging characteristics are summarized in Tables 1 and 2.

ACE was elevated in 62% of the patients in which it was measured (n = 10/16). Creatinine, vitamin D 25-OH, calcium, and phosphorus did not show significant alterations. During the diagnostic process, 23 biopsies were performed, of which 95% showed granulomas with noncaseating necrosis. Most patients (76%) were controlled with prednisolone, average dose of 20 mg (7.5–50 mg) per day (Table 3).

Discussion

Sarcoidosis is a multisystemic granulomatous disease of unclear etiology that has a global distribution, is more frequent in women with 45% to 65% of cases. We also found a higher frequency in women (73%). The age at diagnosis was 36–55 years in both gender, though men were diagnosed approximately 10 years earlier than women in average, which agrees with findings from other publications worldwide.

The clinical presentation of sarcoidosis includes a spectrum of manifestations that vary from asymptomatic, slow progression and forms with severe organ damage. This great clinical variability, added to the multisystem involvement, adds to the disease a high uncertainty, which slows its diagnostic process. However, in recent years, great advances have been made in the diagnostic approach of the disease, so that the time until diagnosis has been significantly shortened in wealthy countries, reaching an average diagnostic delay of less than 6 months in 70% of cases. However, despite what has been observed in other countries and in Colombia, in our series there was an average diagnos-
tific delay of 1 year, reaching up to 2 years in some cases. In a study conducted in Turkey on 293 patients,\(^{15}\) the disease was diagnosed in an average of 3 months, which short time was attributed to the high tendency to perform chest X-ray as a routine procedure.\(^{15}\)

Generally, the manifestations of sarcoidosis vary according to ethnicity, age, sex, and geographic area.\(^{9,15}\) Among the clinical manifestations initially shown by our patients, erythema nodosum, arthritis, and cough were present in up to one-third. Unfortunately, few studies mention the initial symptoms of patients with sarcoidosis. A study conducted in 640 patients in Barcelona\(^{36}\) found a frequency of erythema nodosum as an initial manifestation similar to that of our series. However, pulmonary and articular symptoms as initial manifestations were only present in 15% and 11% of their cases, respectively. Therefore, it is noteworthy that in our population joint manifestations as an initial symptom were more common than in other analyzed cohorts.

Lung compromise is the most frequent in sarcoidosis,\(^{9,26,31}\) the frequency of lung involvement in North American, European, and Asian cohorts ranges from 85% to 99%.\(^{12-16,18}\) We observed a lower frequency (64%). Along the same lines, we found three Colombian studies\(^{21-23}\) of 8, 22, and 51 patients, respectively, that also showed a lower frequency of lung involvement (50%, 56–69%, and 48). Another study carried out in Brazil, with 100 patients, also showed a lower frequency (66%).\(^{20}\) It is possible that these findings in Latin America may be associated with the few and small series conducted in the region, but it cannot be ruled out that it may be associated with different genetic and/or environmental factors in the Latin American population compared to the rest of the world. Therefore, studies with greater numbers of patients are necessary to confirm this.

Cough is the most common symptom and can vary from 15%\(^{15}\) to 80%\(^{15}\) according to the population. In our patients, cough was the most frequent pulmonary symptom, being observed in 50% of those with confirmed pulmonary sarcoidosis and being frequently associated with extrapulmonary manifestations. Dyspnea was seen in 13%, similar than was observed in the Chinese population.\(^{15}\) Chest pain was seen in only one case in our series, which differs from other studies where pain has been more frequent, ranging from 10 to 20% of cases.\(^{13,15}\)

Chest CT is not always necessary and is indicated mainly when there are difficulties in the diagnosis of atypical presentations or in the identification of complications such as pulmonary fibrosis.\(^{32}\) The most common finding is mediastinal lymphadenopathy, in 80–95% of cases.\(^{33,34}\) This is followed by a nodular pattern at the pulmonary level, at 75–100%.\(^{31,34,35}\) As in other studies, the most frequent chest CT findings in our study were pulmonary nodules and mediastinal adenomegalies; however, they were found at a lower frequency than reported earlier (54% and 50%, respectively). The frequency of lymphadenopathy has reached 100% in other studies, but the

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<td>5 (14.7)</td>
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<td></td>
<td>14 (41.2)</td>
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<tr>
<td></td>
<td>No treatment</td>
</tr>
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<td>4 (11.7)</td>
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frequency of pulmonary nodules that we found was similar
to other populations (50%).

We saw signs of interstitial lung disease (replacement of
lung parenchyma by connective tissue) in 36% of the cases
of pulmonary sarcoidosis (23% of total cases), similar to
other publications in which 20–25% of patients have interstitial
involvement. It progresses to advanced lung disease in up
to 5% of cases, in whom the morbidity and mortality rate are
higher. One of the limitations of our study was the unavail-
ability of lung function tests in most cases.

Although the lungs are the most often compromised sys-
tem in sarcoidosis, granulomatous inflammation can affect
any organ, leading to extrapulmonary manifestations that
sometimes end in severe organ damage and death, especially
in cases of cardiac and neurological involvement.

According to different series carried out worldwide, extrapu-
lmonary manifestations may be present in 40–60% of
cases. However, in our cohort, the frequency was higher,
at 85% of cases.

After the lungs, the skin was the most affected organ in this
series, being compromised in half of the cases (50%). Erythema
nodosum was the most common cutaneous manifestation. As
with other clinical variables, our cohort showed a higher fre-
cuency of skin involvement than other cohorts, where skin
involvement (although it also has ranked first) has been found
in lower numbers, varying from 13% in China to 20–25% in
North America/Europe and 32–37% in Turkey.

Ophthalmic involvement was the second manifestation in
frequency, seen in one-third of our patients (32%). This
occurred more frequently in Colombia than in other countries,
where it ranges between 1% and 23%, including Latin American
countries. We also observed musculoskeletal involvement in one-third of cases (32%), similar to available worldwide data.
However, the frequency of these manifestations is less than 15% in North America and China. Upper respiratory tract involvement and neurological mani-
festations were present in 17% and 14% of our cases,
respectively, different from the <10% reported in other series
around the world.

Lymphatic involvement was similar in proportion to that
observed in other cohorts (17%). This is striking since it is the only system whose frequency remains constant in different world populations. It is important to
recall the association with lymphoma in these cases, termed
sarcoidosis–lymphoma syndrome.

The least affected systems in this study were the renal,
cardiac, and splenic systems (<5%), a frequency similar to
that in other populations. It should be noted we the frequency of liver involvement,
other system commonly affected (12–20% of patients with
sarcoidosis).

Multiple serological biomarkers have been proposed for
the diagnosis and monitoring of sarcoidosis. ACE has been
a widely studied molecule since the last century. It is ele-
vated during sarcoidosis because this enzyme is secreted by
monocytes, macrophages, and epithelioid cells that constit-
tute granulomas, so its increase or decrease could be useful
in the diagnosis and monitoring of the disease. Despite
this pathophysiological approach, in practice, multiple
studies have shown limited application, showing a sensitivity
that varies from 41–100% and a specificity of 83–99%. Our
results found that in the patients in whom the ACE level was
measured, it was positive in 62% of them. Therefore, its measure-
ment as a first confirmatory test of sarcoidosis has been
ruled out. However, its usefulness has been postulated as an
additional test to support the diagnosis of sarcoidosis along
with other clinical data. The decision to measure ACE
must be made by considering its cost-effectiveness.

Patients with sarcoidosis have a greater tendency to
develop hypercalcemia and/or hypercalcuria. The cause of
these calcium disorders is secondary to the fact that
macrophages, present in granulomas, have a higher expres-
sion of the enzyme 1-alpha-hydroxylase, which converts
25-hydroxyvitamin-D into 1,25-dihydroxyvitamin-D (active form of vitamin D), leading to increased intestinal absorp-
tion and renal excretion of calcium, ultimately resulting in
hypercalcemia and hypercalcuria, respectively. However, the incidence of hypercalcemia in sarcoidosis is very low,
at most 20%. This agrees with our study, where no alter-
ation in calcium or vitamin D level was observed in our
patients. Despite its low incidence, the calcium test is rec-
commended given that its presence is related to an increased
risk of nephrocalcinosis, nephrolithiasis, and kidney injury,
which are preventable with corticosteroid treatment, which
can improve calcium levels by decreasing the circulation of
the active form of vitamin D.

Regarding the treatment of sarcoidosis, not all cases
require pharmacological management because in many cases,
the disease may be asymptomatic or present with mild clin-
ical manifestations without risk of causing severe organ
damage and/or with a high probability of spontaneous remission. The decision to initiate treatment is based on
the presence and severity of pulmonary manifestations and
pulmonary imaging and function findings. With respect to
extrapulmonary symptoms, it becomes mandatory to estab-
lish treatment when ocular, neurological, cardiac, renal,
hepatic, splenic, hypercalcemia, disfiguring cutaneous
manifestations, or other manifestations that decrease patient
quality of life present. Once treatment is established, a
disease remission rate of up to 60% is observed within the first
10 years.

The first-line treatment is oral corticosteroids, followed
by second-line management (methotrexate, azathioprine,
mycophenolate mofetil, leflunomide, cyclophosphamide,
hydroxychloroquine) that is indicated in case of intolerance
to steroids or refractory disease progression. In our cohort,
88% of patients required pharmacological treatment, while
the other 12% had spontaneous disease remission without
treatment. This was similar to other Latin American and
European and North American series, where the propor-
tion of patients requiring treatment was 43–55%. Of
the patients who required treatment in our cohort, steroids
(prednisolone) controlled the disease in 76% of them, at
an average dose of 20 mg (7.5–50 mg) per day, indicating that sar-
coïdosis usually does not require treatment with high steroid
doses. Methotrexate was the most used second-line drug
(26%), followed by azathioprine (17%). In other series, second-
line drugs were used in fewer than 12% of cases. A total
of 15% of patients needed biologics and used etanercept
and adalimumab, a rate similar to that in a European cohort.
Conclusion

In the studied cohort, sarcoidosis was more frequent in women and in mestizos, and it presented earlier in men. The delay from symptom onset to disease diagnosis was approximately 12 months, confirming the difficulty of this diagnosis. Half of the patients initially showed both clinical and radiological pulmonary manifestations, and the majority had variable degrees of extrapulmonary involvement. Elevated ACE was not correlated with extrapulmonary involvement; neither the calcium-phosphorus profile nor the antinuclear antibodies were useful to establish the presence of sarcoidosis.

Study limitations

This study presents some weaknesses related to its retrospective nature, such as the low number of patients, the absence of histological confirmation for all cases, the non-inclusion of the classification of the chest X-ray findings, and the lack of information about pulmonary function in most medical records.

Conflict of interests

The authors declare that they have no competing interests.

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