Revista Colombiana de
REUMATOLOGÍA

www.elsevier.es/rcreuma

Original Investigation

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

Mario Bautista-Vargas[a,b], *Germán Puerta*[a,b], *Diego Fernando Scarpetta-González*[c], *Juan-David Marín*[d], *Nicolás Salazar-Otoya*[c], *Ivana Nieto-Aristizábal*[a,e], *David Aguirre-Valencia*[a,f,*]

[a] *Research Group in Rheumatology, Autoimmunity and Translational Medicine (GIRAT), Valle del Lili Foundation, Icesi University, Cali, Colombia*
[b] *Rheumatology Unit, Department of Internal Medicine, School of Medicine, Icesi University, Cali, Colombia*
[c] *Department of Internal Medicine, School of Medicine, Icesi University, Cali, Colombia*
[d] *School of Medicine, Icesity University, Cali, Colombia*
[e] *Clinical Research Center, Valle del Lili Foundation, Cali, Colombia*
[f] *Rheumatology Unit, Department of Internal Medicine, Valle del Lili Foundation, Cali, Colombia*

ARTICLE INFO

Article history:
Received 14 October 2020
Accepted 8 March 2021

Keywords:
Sarcoidosis
Sarcoidosis, pulmonary
Epidemiology
Granulomatous disease, chronic
Characterization

ABSTRACT

Introduction: 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.

* *Corresponding author.*
E-mail addresses: davidaguirremd@gmail.com, david.aguirre@fvl.org.co (D. Aguirre-Valencia).

Conclusions: Sarcoidosis was more frequent in women and mestizos, and it presented earlier in men. Elevated ACE was not associated with extrapulmonary involvement. Calcium-phosphorus profile and antinuclear antibodies were not useful to establish the diagnosis.

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

Palabras clave:
Sarcoidosis
Sarcoidosis pulmonar
Epidemiología
Enfermedad granulomatosa crónica
Caracterización

R E S U M E N

Introducción: 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 clínico-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.

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.[1] 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,[5] and in individuals exposed to environmental triggers.[6,7] 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

incidence among chronic interstitial lung diseases,[9] and can occur at any point of the disease.[10] Patients may be diagnosed incidentally by chest imaging or may have a chronic presentation with nonspecific symptoms.[6] 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.[9,10] The disease can also affect other organs, such as the heart, liver, skin, eyes, musculoskeletal system, central nervous system, and/or upper airway.[3] 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%.[11]

Although there are reviews about the epidemiological and clinical associations of sarcoidosis, especially in Europe, Asia, and North America,[12–18] studies in the Latin American population are scarce.[19,20] Specifically in Colombia, there are only two recent reports with small sample groups[21,22] and a report on 51 patients published in 1977.[23] 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.

Table 1 – Demographic characteristics of patients with sarcoidosis.

Characteristic	
Age at diagnosis	Median (IQR)
Overall	50 (36–55)
Female	53 (37–57)
Male	40 (32–49)
Sex	*n* (%)
Female	25 (73.5)
Male	9 (26.5)
Ethnicity	*n* (%)
Mestizo	28 (85)

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.[4,12,18,24] 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.[4,14–18,24,25]

The clinical presentation of sarcoidosis includes a spectrum of manifestations that vary from asymptomatic, slow progression and forms with severe organ damage.[26] This great clinical variability, added to the multisystem involvement, adds to the disease a high uncertainty, which slows its diagnostic process.[27] However, in recent years, great advances have been made in the diagnostic approach of the disease,[28–30] 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.[12,14–16] However, despite what has been observed in other countries and in Colombia,[22] in our series there was an average diagnos-

Table 2 – Clinical and imaging characteristics of patients with sarcoidosis.

Characteristic	
Initial symptoms	*n* (%)
Erythema nodosum	11 (33.3)
Arthritis	10 (30.3)
Cough	9 (27.3)
Lymphadenopathy	3 (9.1)
Fatigue	3 (9.1)
Diagnostic delay (months) (Median (IQR)	12 (6–24)
Involvement by system	*n* (%)
Pulmonary	22 (64.7)
Symptoms	
Cough	11 (50.0)**
Dyspnea	3 (13.6)**
Chest pain	1 (4.5)**
*Chest CT findings**	
Pulmonary nodules	12 (54.5)**
Mediastinal lymphadenopathy	11 (50.0)**
Interstitial lung disease	8 (36.3)**
CT not performed	1 (4.5)**
Extrapulmonary	29 (85.3)
Cutaneous	17 (50)
Ophthalmic	11 (32.3)
Musculoskeletal	11 (32.3)
Lymphatic	6 (17.6)
Upper respiratory tract	6 (17.6)
Neurological	5 (14.7)
Renal	2 (5.8)
Cardiac	1 (2.9)
Splenic	1 (2.9)

CT: computed tomography.
* 28 patients underwent CT, but seven had no findings and were classified within the extrapulmonary sarcoidosis group.
** Percentages were calculated based on the 22 patients with pulmonary sarcoidosis.

Table 3 – Paraclinical and histopathological findings of patients with sarcoidosis.

Characteristic	
Angiotensin-converting enzyme (n = 16)	*n* (%)
Elevated	10 (62.5)
Other laboratory tests	Median (IQR)
Creatinine	0.74 (0.65–1)
Blood urea nitrogen	13.6 (9.2–18.5)
Serum calcium	9.39 (9.09–0–55)
Phosphorus	3.87 (3.3–4.4)
Vitamin D 25-OH	24.2 (21–29.89)
Antinuclear antibodies	*n* (%)
Negative	28 (82)
Histopathological findings (n = 23)	*n* (%)
Lung biopsies	1 (4.3)
Extrapulmonary biopsies	22 (95.6)
Skin	10 (43.4)
Lymphadenopathy	6 (26)
Other tissues	6 (26)
Noncaseating granulomas in biopsies	22 (95.6)
Treatment	*n* (%)
Steroids	26 (76.5)
Methotrexate	9 (26.5)
Azathioprine	6 (17.6)
Antimalarials	4 (11.7)
Mycophenolate	1 (2.9)
Biologics	5 (14.7)
Other treatments	14 (41.2)
No treatment	4 (11.7)

tic 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.[9,10] 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[16] 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 89% 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%[16] to 80%[13] 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.[13] 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

frequency of pulmonary nodules that we found was similar than other populations (50%).[15]

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.[31,36] It progresses to advanced lung disease in up to 5% of cases, in whom the morbidity and mortality rate are higher.[31] One of the limitations of our study was the unavailability of lung function tests in most cases.

Although the lungs are the most often compromised system in sarcoidosis, granulomatous inflammation can affect any organ, leading to extrapulmonary manifestations that sometimes end in severe organ damage and death,[37] especially in cases of cardiac and neurological involvement.[35] According to different series carried out worldwide, extrapulmonary manifestations may be present in 40–60% of cases,[13,15,18] 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 frequency 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[13] to 20–25% in North America/Europe[12,16,18] and 32–37% in Turkey.[15,38]

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%,[12,13,15,16,18] including Latin American countries.[20] We also observed musculoskeletal involvement in one-third of cases (32%), similar to available worldwide data.[39,40] However, the frequency of these manifestations is less than 15% in North America and China.[12,13,18] Upper respiratory tract involvement and neurological manifestations were present in 17% and 14% of our cases, respectively, different from the <10% reported in other series around the world.[12,16,18,41]

Lymphatic involvement was similar in proportion to that observed in other cohorts (17%).[12,13,16,18,20] 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.[42]

The least affected systems in this study were the renal, cardiac, and splenic systems (<6%), a frequency similar to that in other populations.[12,13,16,18] It should be noted we did not evaluate the frequency of liver involvement, another system commonly affected (12–20% of patients with sarcoidosis).[12,16,18]

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 elevated during sarcoidosis because this enzyme is secreted by monocytes, macrophages, and epithelioid cells that constitute granulomas,[43] so its increase or decrease could be useful in the diagnosis and monitoring of the disease.[7,44] 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%.[44] Our results found that in the patients in whom the ACE level was measured, it was positive in 62% of them. Therefore, its measurement as a single 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.[34,44] The decision to measure ACE must be made by considering its cost-effectiveness.[45]

Patients with sarcoidosis have a greater tendency to develop hypercalcemia and/or hypercalciuria. The cause of these calcium disorders is secondary to the fact that macrophages, present in granulomas, have a higher expression 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 absorption and renal excretion of calcium, ultimately resulting in hypercalcemia and hypercalciuria, respectively.[46] However, the incidence of hypercalcemia in sarcoidosis is very low, at most 20%.[47] This agrees with our study, where no alteration in calcium or vitamin D level was observed in our patients. Despite its low incidence, the calcium test is recommended given that its presence is related to an increased risk of nephrocalcinosis, nephrolithiasis, and kidney injury,[46] which are preventable with corticosteroid treatment, which can improve calcium levels by decreasing the circulation of the active form of vitamin D.[48]

Regarding the treatment of sarcoidosis, not all cases require pharmacological management because in many cases, the disease may be asymptomatic or present with mild clinical manifestations without risk of causing severe organ damage and/or with a high probability of spontaneous remission.[1,49] 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 establish treatment when ocular, neurological, cardiac, renal, hepatic, splenic, hypercalcemia, disfiguring cutaneous manifestations, or other manifestations that decrease patient quality of life present.[6,49,50] Once treatment is established, a disease remission rate of up to 60% is observed within the first 10 years.[50]

The first-line treatment is oral corticosteroids,[49] 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.[1,7] 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 data[19] but higher than in European and North American series, where the proportion of patients requiring treatment was 43–55%.[12,16] 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 sarcoidosis 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.[16,19] A total of 15% of patients needed biologics and used etanercept and adalimumab, a rate similar to that in a European cohort.[19]

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.

REFERENCES

1. Jain R, Yadav D, Puranik N, Guleria R, Jin JO. Sarcoidosis: causes, diagnosis, clinical features, and treatments. J Clin Med. 2020;9, http://dx.doi.org/10.3390/jcm9041081.
2. Sheng W, Loke J, Herbert C, Thomas PS. Sarcoidosis: immunopathogenesis and immunological markers. Int J Chronic Dis. 2013;2013, http://dx.doi.org/10.1155/2013/928601.
3. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. N Engl J Med. 2007;357, http://dx.doi.org/10.1056/NEJMra071714.
4. Erdal BS, Clymer BD, Yildiz VO, Julian MW, Crouser ED. Unexpectedly high prevalence of sarcoidosis in a representative U.S. Metropolitan population. Respir Med. 2012;106:893–9, http://dx.doi.org/10.1016/j.rmed.2012.02.007.
5. Rossman MD, Thompson B, Frederick M, Maliarik M, Iannuzzi MC, Rybicki BA, et al. HLA-DRB11101: a significant risk factor for sarcoidosis in blacks and whites. Am J Hum Genet. 2003;73:720–35, http://dx.doi.org/10.1086/378097.
6. Llanos O, Hamzeh N. Sarcoidosis. Med Clin North Am. 2019;103:527–34, http://dx.doi.org/10.1016/j.mcna.2018.12.011.
7. Grunewald J, Grutters JC, Arkema EV, Saketkoo LA, Moller DR, Müller-Quernheim J. Sarcoidosis. Nat Rev Dis Prim. 2019;5, http://dx.doi.org/10.1038/s41572-019-0096-x.
8. Rybicki BA, Major M, Popovich J, Maliarik MJ, Iannuzzi MC. Racial differences in sarcoidosis incidence: a 5-year study in a health maintenance organization. Am J Epidemiol. 1997;145:234–41, http://dx.doi.org/10.1093/oxfordjournals.aje.a009096.
9. Valeyre D, Bernaudin JF, Jeny F, Duchemann B, Freynet O, Planès C, et al. Pulmonary sarcoidosis. Clin Chest Med. 2015;36:631–41, http://dx.doi.org/10.1016/j.ccm.2015.08.006.
10. Valeyre D, Prasse A, Nunes H, Uzunhan Y, Brillet PY, Müller-Quernheim J. Sarcoidosis. Lancet. 2014;383:1155–67, http://dx.doi.org/10.1016/S0140-6736(13)60680-7.
11. Saidha S, Sotirchos ES, Eckstein C. Etiology of sarcoidosis: does infection play a role? Yale J Biol Med. 2012;85:133–41.
12. Judson MA, Boan AD, Lackland DT. The clinical course of sarcoidosis: presentation, diagnosis, and treatment in a large white and black cohort in the United States. Sarcoidosis Vasc Diffus Lung Dis. 2012;29:119–27.
13. 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;8:e018865, http://dx.doi.org/10.1136/bmjopen-2017-018865.
14. Fernández González S, López González R. Epidemiología, formas de presentación, estadio radiológico y métodos diagnósticos de la sarcoidosis en el área de León (2001–2008). Rev Clin Esp. 2011;211:291–7, http://dx.doi.org/10.1016/j.rce.2011.03.001.
15. Kıter G, Müsellim B, Cetinkaya E, Türker H, Kunt Uzaslan AE, Yentürk E, et al. Clinical presentations and diagnostic work-up in sarcoidosis: a series of Turkish cases (clinics and diagnosis of sarcoidosis). Tuberk Toraks. 2011;59:248–58.
16. Mañá J, Rubio-Rivas M, Villalba N, Marcoval J, Iriarte A, Molina-Molina M, et al. Multidisciplinary approach and long-term follow-up in a series of 640 consecutive patients with sarcoidosis. Medicine (United States). 2017;96:e7595.
17. Gerke AK, Judson MA, Cozier YC, Culver DA, Koth LL. Disease burden and variability in sarcoidosis. Ann Am Thorac Soc. 2017;14 Suppl 6:421–8, http://dx.doi.org/10.1513/AnnalsATS. 201707-564OT.
18. Baughman RP, Teirstein AS, Judson MA, Rossman MD, Yeager H, Bresnitz EA, et al. Clinical characteristics of patients in a case control study of sarcoidosis. Am J Respir Crit Care Med. 2001;164:1885–9, http://dx.doi.org/10.1164/ajrccm.164.10.2104046.
19. Gonzalez EL, Vigliano C, Caneva J. Sarcoidosis. Presentacion clínica y pronóstico. Medicina. 2010;70:499–502.
20. Lemos-Silva V, Araújo PB, Lopes C, Rufino R, Costa CH. Características epidemiológicas de pacientes com sarcoidose na cidade do Rio de Janeiro. J Bras Pneumol. 2011;37:438–45, http://dx.doi.org/10.1590/S1806-37132011000400005.
21. Santamaria-Alza Y, Fajardo J. Sarcoidosis: una serie de casos del nororiente colombiano. Neumol Cir Torax. 2017;76:14–6.
22. Muñoz C, Restrepo-Escobar M, Martínez-Muñoz M, Echeverri A, Márquez J, Pinto LF. Differences between patients with sarcoidosis with and without joint involvement treated for fifteen years in a third level hospital. Reumatol Clin. 2020;16:45–8, http://dx.doi.org/10.1016/j.reuma.2018.01.001.
23. Valovis R. Sarcoidosis. Estudio clinico de 51 casos y revision de la literatura. Acta Med Colomb. 1977;2:101–10.
24. Arkema EV, Cozier YC. Epidemiology of sarcoidosis: current findings and future directions. Ther Adv Chronic Dis. 2018;9:227–40, http://dx.doi.org/10.1177/2040622318790197.
25. Baughman RP, Field S, Costabel U, Crystal RG, Culver DA, Drent M, et al. Sarcoidosis in America: analysis based on health care use. Ann Am Thorac Soc. 2016:1244–52, http://dx.doi.org/10.1513/AnnalsATS. 201511-760OC.
26. Judson MA. The clinical features of sarcoidosis: a comprehensive review. Clin Rev Allergy Immunol. 2015;49:63–78, http://dx.doi.org/10.1007/s12016-014-8450-y.
27. Valeyre D, Bernaudin JF, Uzunhan Y, Kambouchner M, Brillet PY, Soussan M, et al. Clinical presentation of sarcoidosis and diagnostic work-up. Semin Respir Crit Care Med. 2014;35:336–51, http://dx.doi.org/10.1055/s-0034-1381229.
28. Judson MA, Costabel U, Drent M, Wells A, Maier L, Koth L, et al. The WASOG sarcoidosis organ assessment instrument: an update of a previous clinical tool. Sarcoidosis Vasc Diffus Lung Dis. 2014;31:19–27.
29. Bickett AN, Lower EE, Baughman RP. Sarcoidosis diagnostic score: a systematic evaluation to enhance the diagnosis of sarcoidosis. Chest. 2018;154:1052–60, http://dx.doi.org/10.1016/j.chest.2018.05.003.

30. Crouser ED, Maier LA, Wilson KC, Bonham CA, Morgenthau AS, Patterson KC, et al. Diagnosis and detection of sarcoidosis. An official American Thoracic Society clinical practice guideline. Am J Respir Crit Care Med. 2020;201:e26–51, http://dx.doi.org/10.1164/rccm.202002-0251ST.
31. Spagnolo P, Rossi G, Trisolini R, Sverzellati N, Baughman RP, Wells AU. Pulmonary sarcoidosis. Lancet Respir Med. 2018;6:398–402, http://dx.doi.org/10.1016/S2213-2600(18)30064-X.
32. Lynch JP. Computed tomographic scanning in sarcoidosis. Semin Respir Crit Care Med. 2003;24:393–418, http://dx.doi.org/10.1055/s-2003-42375.
33. Keijsers RG, Veltkamp M, Grutters JC. Chest imaging. Clin Chest Med. 2015;36:603–19, http://dx.doi.org/10.1016/j.ccm.2015.08.004.
34. Chavarriaga-Restrepo A, López-Amaya JE, Mesa-Navas MA, Velásquez-Franco JC. Sarcoidosis: muchas caras, una enfermedad. Revisión narrativa de la literatura. Iatreia. 2019;32:191–203, http://dx.doi.org/10.17533/udea.iatreia.11.
35. Martínez MJ, Palacios KM, Astorga MM, Conde Blanco M, Ferrario MC, Aguirre PM. Sarcoidosis al descubierto: Lo que deberíamos informar en las imágenes torácicas. Rev Argent Radiol. 2019;83:77–86.
36. Patterson KC, Strek ME. Pulmonary fibrosis in sarcoidosis clinical features and outcomes. Ann Am Thorac Soc. 2013:362–70, http://dx.doi.org/10.1513/AnnalsATS. 201303-069FR.
37. Judson MA. Extrapulmonary sarcoidosis. Semin Respir Crit Care Med. 2007;28:83–101, http://dx.doi.org/10.1055/s-2007-970335.
38. Yanardağ H, Pamuk ON, Karayel T. Cutaneous involvement in sarcoidosis: analysis of the features in 170 patients. Respir Med. 2003;97:978–82, http://dx.doi.org/10.1016/s0954-6111(03)00127-6.
39. Nessrine A, Zahra AF, Taoufik H. Musculoskeletal involvement in sarcoidosis. J Bras Pneumol. 2014;40:175–82, http://dx.doi.org/10.1590/s1806-37132014000200012.
40. Bufort MG, Pascual EV, Morales CM, Guerrero MR, Ubiaga CI, Golmar AC, et al. Study of articular sarcoidosis in a tertiary care hospital. Ann Rheum Dis. 2017:719, http://dx.doi.org/10.1136/annrheumdis-2017-eular.6674.
41. Rottoli P, Bargagli E, Chidichimo C, Nuti D, Cintorino M, Ginanneschi C, et al. Sarcoidosis with upper respiratory tract involvement. Respir Med. 2006;100:253–7, http://dx.doi.org/10.1016/j.rmed.2005.04.018.
42. Aguirre-Valencia D, Valencia Maturana J, Londoño Tabares S, Bravo JC, Tobón GJ, Vásquez GM. Sarcoidosis-lymphoma syndrome. Presentation of 2 clinical cases. Rev Colomb Reumatol. 2020;27:297–302, http://dx.doi.org/10.1016/j.rcreu.2019.12.003.
43. Ramos-Casals M, Retamozo S, Sisó-Almirall A, Pérez-Alvarez R, Pallarés L, Brito-Zerón P. Clinically-useful serum biomarkers for diagnosis and prognosis of sarcoidosis. Expert Rev Clin Immunol. 2019;15:391–405, http://dx.doi.org/10.1080/1744666X. 2019.1568240.
44. Chopra A, Kalkanis A, Judson MA. Biomarkers in sarcoidosis. Expert Rev Clin Immunol. 2016;12:1191–208, http://dx.doi.org/10.1080/1744666X. 2016.1196135.
45. Alston C, Hull R, Sinclair D, Ledingham J, McCrae F, Shaban R, et al. Serum ACE for sarcoidosis is not such an ACE test. Ann Rheum Dis. 2013;72. A330.2–A330.
46. Sharma OP. Vitamin D, calcium, and sarcoidosis. Chest. 1996;109:535–9, http://dx.doi.org/10.1378/chest.109.2.535.
47. Adams JS, Sharma OP, Gacad MA, Singer FR. Metabolism of 25-hydroxyvitamin D3 by cultured pulmonary alveolar macrophages in sarcoidosis. J Clin Invest. 1983;72:1856–60, http://dx.doi.org/10.1172/JCI111147.
48. Bell NH, Stern PH, Pantzer E, Sinha TK, DeLuca HF. Evidence that increased circulating 1α,25-dihydroxyvitamin D is the probable cause for abnormal calcium metabolism in sarcoidosis. J Clin Invest. 1979;64:218–25, http://dx.doi.org/10.1172/JCI109442.
49. Baughman RP, Nunes H, Sweiss NJ, Lower EE. Established and experimental medical therapy of pulmonary sarcoidosis. Eur Respir J. 2013;41:1424–38, http://dx.doi.org/10.1183/09031936.00060612.
50. Moor CC, Kahlmann V, Culver DA, Wijsenbeek MS. Comprehensive care for patients with sarcoidosis. J Clin Med. 2020;9:390, http://dx.doi.org/10.3390/jcm9020390.