UNIVERSIDAD DE ANTIOQUIA
Facultad de Medicina
IATREIA
Revista M
Medical Journal - University of Antioquia

Sarcoidosis: many faces, one disease. Narrative review of the literature

Andrés Chavarriaga-Restrepo[1], Juan Esteban López-Amaya[2], Miguel Antonio Mesa-Navas[3], Carlos Jaime Velásquez-Franco[4]

[1] Internist, CES Clinic, Medellin, Colombia.

[2] Radiologist, Bolivarian University Clinic, Medellin, Colombia.

[3] Teacher, School of Health Sciences, Universidad Pontificia Bolivariana (Pontifical Bolivarian University), Medellin, Colombia.

[4] Professor of Internal Medicine, School of Health Sciences. Universidad Pontificia Bolivariana (Pontifical Bolivarian University), Rheumatology Section. Bolivarian University Clinic. Medellin Colombia.

Correspondence: Andrés Chavarriaga-Restrepo; andresch_1@hotmail.com

Received: March 31, 2018

Accepted: August 31, 2018

References: Chavarriaga-Restrepo A, López-Amaya JE, Mesa-Navas MA, Velásquez-

Franco CJ. Sarcoidosis: many faces, one disease. Narrative review of the literature. Latreia In press. DOI 10.17533/udea.iatreia.11.

SUMMARY

Sarcoidosis is a systemic granulomatous disease of unknown etiology. It affects patients of all types and ages, being more frequent between the third and fourth decade of life with a second peak around fifth decade in the Scandinavian and Japanese populations. It is more common in women and severe in the Afro-descendant population. Antigens that initiate this granulomatous response are unknown, however, they are presumed to be airborne as a result of the lung involvement high frequency in this disease. Its clinical manifestation covers a wide range of manifestations, including acute and limited forms to chronic with progressive organ damage and death. Its diagnosis is based on the existence of non-caseating granulomas in tissues, excluding other diseases such as mycobacterial infection.

KEYWORDS

Lymphadenopathy; Lung; Sarcoidosis

RESUMEN

Sarcoidosis: muchas caras, una enfermedad. Revisión narrativa de la literatura

La sarcoidosis es una enfermedad granulomatosa sistémica de etiología desconocida. Esta puede afectar a pacientes de todas las latitudes y edades, siendo más frecuente entre la tercera y cuarta década de la vida con un segundo pico alrededor de los 50 años en las poblaciones

escandinava y japonesa. Es más frecuente en mujeres y grave en la población afrodescendiente. Los antígenos que inician esta respuesta granulomatosa son desconocidos, pero se presume que son aerotransportados por la alta frecuencia de compromiso pulmonar en esta enfermedad. Su presentación clínica abarca una amplia gama de manifestaciones, desde formas agudas y limitadas hasta el compromiso crónico con daño orgánico progresivo y muerte. Su diagnóstico se basa en la existencia de los granulomas no caseificantes en los tejidos, con la exclusión de otras enfermedades, entre ellas infección por micobacterias.

PALABRAS CLAVE

Linfadenopatía; Pulmón; Sarcoidosis

INTRODUCTION

Sarcoidosis is a systemic granulomatous disease of unknown etiology and global distribution (1). Its diagnosis is based on the exclusion of other diseases which can cause granulomas with non-caseating necrosis, added to the involvement of at least two organs in patient with compatible symptoms (2).

Its origin dates back to 1899, when Boeck gave the name to multiple benign sarcoid injuries in the extensor regions of the upper limbs of a 36-year-old policeman. The presence of epithelioid cells with a large and pale nucleus was found in the microscopic analysis, associated with some giant cells which had a sarcoma appearance, which is the reason why this name was given at that time and it is preserved until today (3).

In recent years there has been a breakthrough in knowledge about the physiopathology, clinical manifestations and treatment of the disease; and we will address some of them

during the following review.

EPIDEMIOLOGY

From the epidemiological standpoint, the sarcoidosis disease can affect patients of all types and ages, it is more frequent between the third and fourth decade of life, with a second peak around fifth decade in the Scandinavian and Japanese populations (4, 5). It is 1.5 times more common in women (5), with a reported prevalence of 1-60 out of 100,000 patients that varies according to the location and race of the different reported series, as it is higher in whites and afro-descendants, and three times more frequent in the second one as shown in Table 1 (6).

Table 1. Prevalence by race

Population / Race	Prevalence
U.S	10-40/100.000
African Americans	35,4-60/100.000
whites	10,4-14/100.000
Scandinavian	50-60/100.000
Japan	1-2/100.000
Argentina Brazil	1,5/100.000

Source: reference 18.

It is also important to highlight that there is a variation not just in the prevalence of the disease but in its manifestation form according to the race, being more common the chronic forms and the ocular involvement in the afrodescendant population and the asymptomatic forms in the white population; thus impacting the prognosis of the disease, since the African-American population has a higher demand for steroids and less successful in clearing these. Another described variation is observed in Japan, where there is a higher incidence of a cardiac involvement described in autopsy studies, which is present in up to 50% of patients and is the leading cause of death (4, 5, 7).

In the local epidemiology there are a series of cases of the northeastern of Colombia (8) where 8 patients were included, 50% men with an average age of 40, the most frequent symptoms of the series is dyspnea 75%, followed by cough and weight loss. Lung involvement was observed in 50% of patients, being typically bilateral and upper lobe involvement (8). The Muñoz et al series was also found in Medellin with 22 patients, of whom 89% were women with an average age of 46, with cutaneous and joint symptoms, being the main cause of consultation, with an average symptoms time of 5 months at diagnosis. Fourteen patients had lung symptoms, 14 had skin symptoms determined by erythema nodosum, papules, changes in tattoos and Sweet syndrome and joint symptoms were reported (9) in 62% of patients.

PHYSIOPATHOLOGY

Although the physiopathology of sarcoidosis is not completely clear, it has been considered that its etiology can be triggered by an environmental agent, an antigen that in a susceptible host triggers this granulomatous reaction. Regarding the initial antigen, its identity is unknown, but it is presumed to be airborne, since some type of lung involvement occurs in 95% of the cases (10).

Several studies have been carried out in which genetic material has been found in granulomas, mainly mycobacteria (11), in order to identify this antigen. The above is supported by a study carried out at Johns Hopkins in which 9 patients with sarcoidosis and 14 controls without the disease were compared, in which 55% of the evaluated samples were found to have monoclonal antibodies anti-catalase peroxidase of M. tuberculosis in the sarcoidosis group and in none of the control group (12).

In the study of cases and controls to determine the etiology of sarcoidosis (ACCESS) (13), which recruited 736 patients, other triggering factors associated with certain occupations (poultry breeding, car manufacturing, gardening) and environmental exposures were found (insecticides, birds, cotton, radiation, organic dust, construction material), which reinforces the concept that a variety of antigens can trigger the disease in a patient with genetic susceptibility. Finally, the low socioeconomic status has also been associated with the development of this disease, partly explained by the poor access to health services and partly by the tendency to perform jobs with greater exposure to triggers in this group of people (14, 15).

As a disease, it has a systemic inflammatory component which is presumed to be due to the antigenic occurrance through the major histocompatibility complex with activation of Th1 lymphocytes. These infiltrate the lung and produce cytokines such as alpha Tumor Necrosis Factor (TNF-), the beta Transforming Growth Factor (TGF-) and interleukins 2 and 12, among others; which leads to the formation of granulomas with non-caseating necrosis and local microarchitecture damage (16).

Granulomas are composed of T CD4 lymphocytes (Th1) with activated macrophages, which simulate an epithelioid cell (called epithelioid granulomas), surrounded in turn by fibroblasts, B cells and T CD8 lymphocytes (4).

These epithelioid granulomas are the main source of Angiotensin-Converting Enzyme, described even as a diagnostic aid in the disease.

Granuloma formation is one of the disease's central axes and consists of 4 stages: initiation where macrophages and monocytes are recruited, the first internalize the antigen which they process and present, through the major histocompatibility complex type II to the T CD4

lymphocytes. Subsequently, the accumulation phase where there is an oligoclonal proliferation with a CD4 lymphocyte differentiation and an increase in the number of lymphocytes CD-4, CD-8 and monocytes occurs; followed by an effect phase involving several mediators such as interleukins 2 and 12 and the interferon gamma (IFN-γ). Finally, the future of the granuloma is defined based on the cytokines profile present at that time, in such a way that if antigenic clearance and IL-10 predominates, the route is changed to a Th2 type response with a subsequent limitation of the disease, and if the beta Transforming Growth Factor and cathelicidin 18 predominate, the fibrotic process that eventually will account the damage in the architecture and the dysfunction of the affected organs will be perpetuated (Image 1) (17, 18).

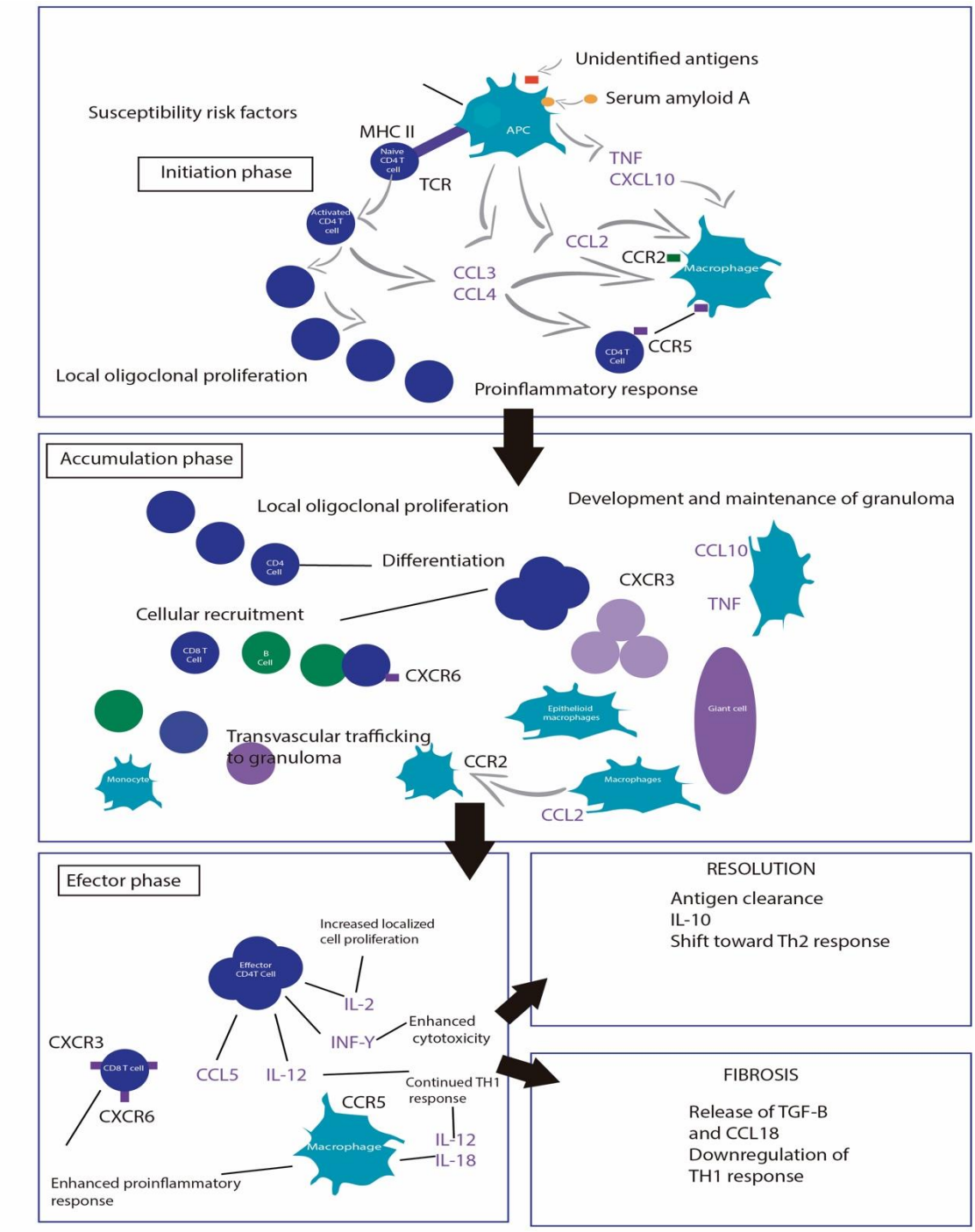


Image 1.Physiopathogenesis Phases Source: reference 6.

CLINICAL MANIFESTATION

As a systemic disease, it can affect any organ with a variable spectrum of manifestations from the asymptomatic forms, going through the self-limited forms of inherently benign course to the chronic forms with accumulated organ damage and a worse prognosis (16). Regarding the asymptomatic forms, they are usually diagnosed incidentally during the performance of a thoracic image, where typical findings of the disease are found given by symmetrical hilar adenopathies; which in 5% of the cases are unilateral or absent adenopathies, (6).

The acute forms are represented prototypically by Löfgren's syndrome, caused by the triad bilateral hilar lymphadenopathy, erythema nodosum and bilateral ankle arthritis. This, together with uveoparotid fever (Heerfordt's syndrome), constitute the two symptomatic scenarios in which it is possible to make the sarcoidosis diagnosis without histological confirmation (19).

The Löfgren syndrome has a similar distribution between men and women, a peak incidence between 30 and 40 years and a second peak in women between 45 and 65 years. Usually, It does not require treatment as it solves itself, which speaks of its good prognosis, being this an unusual form of manifestation in the African-American population (16). Heerfordt syndrome is also a manifestation of good prognosis and consists of the bilateral uveitis and parotitis presence, which is present in 73% of cases. The other typical symptoms completing this syndrome and that are less frequent are fever and facial paralysis (20).

The chronic forms have a worse prognosis and are more frequent in the black race, the mainly affected organ is the lung (90-95%), which can present a wide range of symptoms ranging from cough, dyspnea, occasional wheezing, hemoptysis and chest pain, and even the

involvement of the lung parenchyma with fibrosis (2, 21). This condition is what determines the disease prognosis in the non-Japanese population, due to the poor survival associated with advanced forms (22). Other involved systems in order of frequency are shown in Table 2. Regarding the multi-systemic involvement of the disease, the ACCESS study (13) found that 50% of patients had an organ involvement, 30% two organs and 20% in three or more organs.

Table 2. Organ involvement

Cohort	ACCESS (13)	MUSC (23)	TTS (24)
Number	736	1.582	293
Lung %	95	89	99
Skin %	16	32	16
Eye %	12	23	5
Peripheral lymphadenopathies %	15	12	13
Liver %	12	20	-
Spleen %	7	7	-
Neurological %	5	9	3

Source: adapted from reference 22

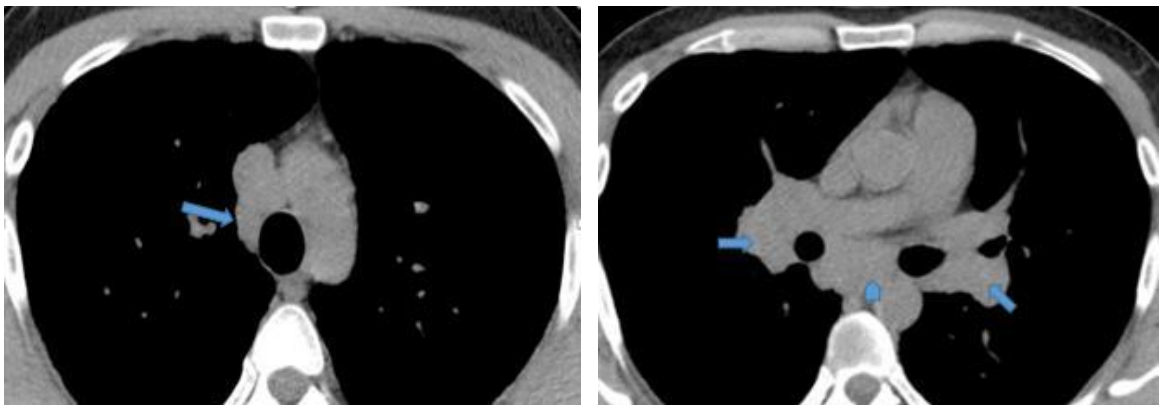
RADIOLOGICAL FINDINGS

More than 40 years ago, Siltzbach developed a sarcoidosis classification system based on a radiological findings pattern that is still widely used and has prognostic value. This classification defines 5 sarcoidosis stages summarized in Table 3. Each stage is related to a spontaneous remission probability that is 60-90% in patients with stage 1 disease, 40-70% with stage 2 disease (Image 2), 10-20% in patients with stage 3 disease and 0% in patients with stage 4 (23, 24).

Table 3. Sarcoidosis Stages based on Radiological Findings

Stage	Findings	Frequency of occurrence
Stage 0	Normal	5 - 10 %
Stage 1	Lymphadenopathies	50 %
Stage 2	Lymphadenopathies and lung infiltrates	25 - 30 %
Stage 3	Lung infiltrates	10 - 12 %
Stage 4	Fibrosis	5 %

Sarcoidosis Classification based on Radiographic findings. Percentages indicate the proportion of patients diagnosed with sarcoidosis and their respective stage at the time of occurrence of the disease.



A **B**

Image 2. 2A. High Resolution Computed Tomography in soft tissue window showing right paratracheal adenopathy. 2B**.** Shows bilateral and symmetrical hilar adenopathies (straight arrows) and conglomerate of subcarinal adenopathies (arrowhead).

This classification system was developed before the introduction of Computed Tomography (CT), and the collected information to date with regard to the prognosis is based on the radiography findings, not on CT. High resolution CT is more sensitive than radiography in the occurrence of subtle abnormalities of lung parenchyma in an early stage of the disease, even in stage 1 (21, 25); however, the prognosis value for tomographic findings has not yet been widely studied (26).

FINDINGS IN HIGH-RESOLUTION COMPUTED TOMOGRAPHY

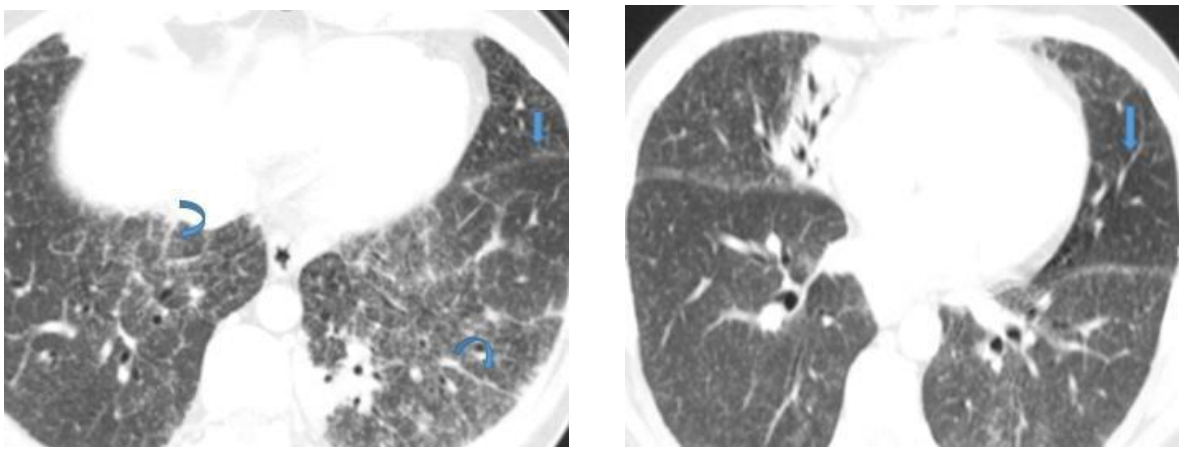
High resolution CT is superior in contrast to the conventional CT in the evaluation and differentiation between inflammation and fibrosis in patients with lung sarcoidosis (27, 28).

Its better spatial resolution improves detection of reticular and nodular shadowing, thickening of interlobular septa and ground-glass opacity or shadowing. High resolution CT also has greater use in the differentiation between active inflammation and irreversible fibrosis in patients with stage 2 or 3 disease. Nodules, ground-glass opacity or shadowing and alveolar shadowing suggest a granulomatous inflammation which can be reversible with therapy (29). In contrast, honeycomb cysts, thick septal bands, distortion of the architecture, loss of volume and traction bronchiectasis indicate an irreversible fibrosis. High resolution tomography can also be useful to check diagnosis in patients with atypical clinical manifestations or with unusual radiological findings (30).

The most common sarcoidosis occurrence corresponds to the presence of right paratracheal and hilar bilateral symmetric adenopathies. Bilateral hilar adenopathies, alone or in combination with mediastinal adenopathies, occur in approximately 95% of patients with sarcoidosis (25, 31); left, subcarinal, aortopulmonary and prevascular paratracheal adenopathies are present in up to 50% of patients (28). Calcifications of the adenopathies are directly related to the duration of the granulomatous disease. They are seen in 3% of patients after 5 years and in 20%, after 10 years; they may have several appearances: amorphous, dotted, in the form of popcorn or egg shell.

Regarding the involvement of the lung parenchyma, the characteristic feature is the perilymphatic distribution of micronodular injuries (75-90% of cases), with a predominantly symmetrical bilateral distribution, although not invariably in the middle and upper areas.

These nodules are usually found in the peribronchovascular interstitium, subpleural and interlobular septa, and can coalesce over time to form larger injuries (macronodules) (Image 3. Sarcoides granulomas also frequently cause nodular or irregular thickening of the peribronchovascular interstitium (29, 30).



A **B**

Image 3. 3A. High resolution CT where micronodules of perilymphatic distribution are evidenced. The involvement in the fissures (straight arrow) and the nodular thickening of interlobular septa (curved arrows) is shown. 2B. Ground glass opacity or shadowing (normal lung parenchyma attenuation indicated by the straight arrow in the lingula). Micronodules with perilymphatic distribution and nodular thickening of interlobular septa that have better representation in 3A are also shown.

Ground-glass Opacity or shadowing occurs in approximately 40% of patients and originates from the confluence of multiple micronodular granulomatous interstitial and fibrotic injuries, which generates compression but not the filling of the air space seen in the alveolitis (25, 27). The mosaic attenuation pattern in patients with sarcoidosis is the result of the involvement of the small airway by granulomas or fibrosis, which may cause an obstruction and be associated to air trapping, the latter is better visualized in the expiratory phases (32, 33).

Finally, fibrotic changes develop by up to 20% of patients can be seen, among which is the presence of thick septal bands, distortion of the architecture, loss of volume, cysts in the honeycomb and traction bronchiectasis, indicative findings of irreversible fibrosis (34). They are more common in the middle and upper lung fields, with a patchy distribution. In advanced cases they can be associated with lung hypertension and / or right heart failure. Other less frequent radiological manifestations will not be addressed in this review.

OTHER CLINICAL MANIFESTATIONS

Ocular involvement due to sarcoidosis is described as the third most frequent in some series among 10-60% of patients (35). It produces an inflammation not only ocular but also in the annexes, occurring more commonly in Afro-descendant women.

Uveitis is the most named involvement, occurs in a heterogeneous manner and is more prevalent in the Japanese population, where it is reported in up to 15% of patients. Its occurrence has two peaks, the first of them in the third decade (usually associated with acute forms) and the second in the sixth or seventh (associated with chronic forms). Its symptoms may include lacrimation, photophobia, and conjunctival pain and injection. However, about one-third of patients with uveitis caused by sarcoidosis have no ocular symptoms (35, 36). It tends to be bilateral and has a preference for the anterior segment in 70 to 85% of the time with panuveitis in 9-30% of cases, the latter being a serious involvement that leads to blindness in 10% of patients, usually within the course of the first year after its debut (35, 37). The second most common involvement is conjunctiva, generally observed as nodules (37). Other less common forms are retinal vasculitis, Heerfordt's syndrome (previously described) and ocular proptosis also called Exophthalmos (38,39), taking into account that any ocular segment can be affected by this disease.

Cutaneous sarcoidosis occurs as the first symptom in 20-35% of patients, and can be a limited form to this organ in 70% of cases. There are specific skin occurrances that require the presence of non-caseating granulomas in the biopsy, and other called non-specific granulomas which do not meet this condition. The most frequent form reported in the literature is erythema nodosum, which is part of nonspecific injuries, in addition to calcifications, acropachy, pyoderma gangrenosum and Sweet syndrome (40). Specific skin

injuries are present in 9-15% of patients with sarcoidosis, represented by papules and plaques, lupus pernio (violaceous plaques), which should not be confused with cutaneous lupus. This injury usually occurs in the nose and cheeks, and represents a poor prognosis as it predicts a progression increased risk to chronic forms of the disease and lung manifestations. Other forms include sarcoidosis in scars, tattoos and subcutaneous nodules or Darier Roussy sarcoidosis (subcutaneous inflammation due to nodules) among others (40).

Joint manifestation due to sarcoidosis can simulate acute or chronic arthropathies, occurs in 25% of patients during the course of the disease. In the series by Muñoz et al., a high presence of arthritis in 62% of the ankles and joints in 59% of the cases was found (9), different than that reported in other Colombian series where half were men and the joint involvement was much lower, close to 8% (40); this difference is mainly explained by reference biases of the aforementioned studies (41). Bilateral arthritis of the ankle is characteristic of this disease, which has a sensitivity of 95% and a specificity of 90% in suspected cases of sarcoidosis (42, 43).

The sarcoidosis prevalence of the nervous system is reported between 3.5-7%, and cranial neuropathy is the most common (47-64%), followed by the central nervous system which is between 14-64% of patients and peripheral manifestations 3-14% (43).

In those patients with systemic disease and neurological symptoms, 60% coincide with the onset, 34% precede it and 6% occur after the onset of symptoms (44).

Renal sarcoidosis is rare and is usually asymptomatic (90% of cases) (45), with the remaining 10% being symptomatic and interstitial nephritis as the most associated (45). Clinically evident cardiac sarcoidosis has been described in 2-7% of patients, with hidden involvement reported in more than 20% of cases; It is important to note that sudden death

may be the initial manifestation (due to rhythm or conduction disorders), which may occur at any time during the illness. It is more typical in the Japanese population with incidences of 50 to 78% in necropsy studies, in which the main cause of death is heart failure (77-85%), unlike other races (13-50%) (7). Difficulties that arise with this form of manifestation are given by the definitive diagnosis, since the Endomyocardial Biopsy has a low performance and the diagnosis is based on non-invasive imaging studies; for which purpose, treatment in the absence of histological diagnosis is authorized s (7).

The hepatic sarcoidosis is underestimated, 11.5% have been described according to the ACCESS study (10), since most of the patients are asymptomatic or their symptoms are not very specific, especially if histological involvement and Hepatic alterations tests are compared in the absence of symptoms. The biopsy is positive in 75% of the patients; and symptoms are usually abdominal pain, pruritus, fever, jaundice and weight loss. Hepatomegaly occurs in 5-15% of patients and the most described biochemical abnormality is the increased of alkaline phosphatase, present in 90% of symptomatic patients (46).

Hematological findings in patients with sarcoidosis are rare, peripheral lymphadenopathies, anemia, thrombocytopenia, chronic disease anemia, lymphopenia and leukopenia have been described, and these findings appear to be due to granulomas in the bone marrow or splenic sequestration (47).

DIAGNOSIS

As a disease, its diagnosis is challenging, since it is eminently discarded (48). For this, three conditions are required: the presence of granulomas non-caseating necrosis (ideally, in at least two organs) (18), discarding diseases with a similar phenotype and a compatible clinical picture (48). At the time of initiating the diagnosis process, the first step is to define whether

there is a multi-systemic involvement, then we must rule out the presence of any of the conditions in which the diagnosis of sarcoidosis can be made without the need of biopsy (as in Löfgren and Heerfordt syndrome) or in the presence of: asymptomatic bilateral hilar adenopathy and in the presence of panda sign and lambda signs on gallium-67 tracing (18). Subsequently, histological confirmation will be sought, giving priority to suspicious injuries easily accessible and, if not possible, the biopsy of mediastinal or hilar adenopathies will be defined. Finally, if there aren't susceptible injuries, it may be useful to perform a blind biopsy in certain tissues as a conjunctiva with 55% positivity (49), salivary gland (20-58%) (50, 51), scalene lymph node (74 -80%) (52) and liver (50-60%) (53).

Historically, the increased levels of Angiotensin-Converting Enzyme (ACE) have been described in the diagnosis of the disease (54). The origin of this association is not entirely clear and seems to be related to the greater increased risk that some genotypes of the ACE confer to the disease.

Its sensitivity and specificity have been calculated in 41.4% and 89.9%, respectively, with a false positive rate of around 10%, so its use is not advisable, as a single test in the diagnosis of this disease (15, 54). Although these limitations are important in patients in whom the differential diagnosis is focused on other granulomatous diseases, the increase twice over the upper limit is highly specific for sarcoidosis and its highest clinical utility could reside there (55). Other aspects that may affect their performance are the family hyperactivity of the ACE, which is associated with high levels above three times the usual reference value in healthy people (56) and steroid treatment that can decrease such values. On the other hand, the usefulness in measuring ACE levels serially to determine the activity of the disease has not been demonstrated yet (55, 57). Other tests which can provide important information include tuberculin, which in patients with active sarcoidosis is generally negative by

peripheral energy, being necessary to clarify that when having a positive tuberculin; tuberculosis should be searched as a cause of symptoms (58).

Some tests that have been discontinued in use include the Kveim Siltzbachm test, in which the tissue preferably from the spleen of a patient with sarcoidosis was used and applied subcutaneously. Subsequently, a biopsy was taken from the site of injury, four to six weeks later, and the formation of granulomas was observed. Although this test had a high sensitivity (87%) for the sarcoidosis diagnosis, the difficulties in obtaining the raw material due to its poor availability have left it aside to be a historical curiosity (59). Another study that has been performed routinely is marked scintigraphy with gallium-67, this test gives a characteristic uptake in the parotid and lacrimal glands "panda sign" and in the mediastinal region with paratracheal and pretracheal involvement "lambda sign".

The presence of these alterations is highly specific for sarcoidosis, however, due to its low sensitivity and poor availability, it is not a test commonly used in the clinical practice (60).

Finally, there are some innovations in the diagnostic models field to try to standardize this process in a disease like this without pathognomonic findings. For this reason the World Association of Sarcoidosis and other Granulomatous Diseases (World Association of Sarcoidosis and other Granulomatous Disorders, WASOG) developed a checklist of organ involvement by sarcoidosis, classifying them as highly probable, probable, possible and undefined (61). This instrument provides a better evaluation, although it doesn’t provide a score that allows to make a decision and which provides a known sensitivity and specificity. Based on this checklist, a diagnostic sarcoidosis score has recently been developed that takes into account the clinical and the histological areas, in addition to providing cutting points with a known sensitivity. Thus, a score of 6 or more in the biopsy area results in a sensitivity of 99.3% and a specificity of 100%; and a score of 3 in the clinical area has a sensitivity of

94.2% and a specificity of 88.8%, which changes to 76.9% and 98.6%, respectively, if the cutting point is modified to 4. Although these findings have not yet been validated by other groups, they could allow a much friendlier approach (62).

DIFFERENTIAL DIAGNOSIS

Among the differential diagnoses it is always necessary to take into account the infectious causes, especially tuberculosis, since this disease is common in our environment (prevalence of 24.1 / 100,000 for 2013) and produces granulomatous injuries.

Other infections to be considered include some fungal infections such as histoplasma, which can also generate granulomas (63). Differential diagnosis usually requires a multidimensional approach where the histological finding must be evaluated by staining and culture to rule out infectious causes (64). The vasculitis associated with antibodies against the neutrophil cytoplasm (ANCA - Antineutrophil cytoplasmic antibodies), especially granulomatosis with polyangiitis, are a mandatory differential, since it induces non-caseating necrosis, lung, ocular and other organs involvement, where the presence of vasculitis in the biopsy will be one of the ways to differentiate it. There are other details in the evolution such as renal involvement, typical of this type of vasculitis, and the positivity of ANCA, especially by ELISA, which are particularly useful to perform this differentiation (14).

Common variable immunodeficiency is another diagnosis to consider, since granulomatous lung disease with lymphocytic infiltration associated with common variable immunodeficiency can be incorrectly diagnosed as sarcoidosis. It is a systemic disease, with lymphadenopathy, splenomegaly, extra and intra-pulmonary granulomatosis, with non-caseating necrosis. In this case, hypogammaglobulinemia and the flat gamma region in

protein electrophoresis guide the diagnosis. Finally, lung findings differ significantly despite similarities in biopsy, therefore, presence of the superior way and adenopathies in sarcoidosis are more frequent (65).

The Sjögren syndrome is part of the differential diagnosis of patients with sarcoidosis, because the parotidomegaly (also called Parotid enlargement) and the involvement of salivary glands and lacrimal glands are part of the described manifestations of the disease.

There is autoimmunity of the exocrine glands in this syndrome, thus producing symptoms such as dry mouth and dry eyes. The coexistence of both diseases has been described, as in the case series of Ramos-Casals (66), in which it is detailed that both diseases share clinical, immunogenetic and pathogeny, what helps to differentiate the presence of antibodies in the Sjögren, usually negative in sarcoidosis, in addition to the salivary gland biopsy where predominance of CD8+ in sarcoidosis and, CD4+ in Sjögren make the difference, even before the doubts in the typical histological findings that may overlap (66).

In recent times, the disease has been described by IgG4 as multisystemic, characterized by the fibroinflammatory involvement of multiple organs: retroperitoneum, salivary glands, pancreas, ganglia, brain, skin, large vessels, among others. Manifested as pancreatitis, sclerosing cholangitis, interstitial nephritis, prostatitis, pneumonia and increased salivary glands (67). The aforementioned characteristics makes difficult to differentiate these two diseases, sometimes IgG4 is mistakenly treated, under the supposed diagnosis of sarcoidosis (68) and there are even reports in the literature of IgG4 pancreatitis with granulomatous involvement in mediastinal ganglia and lung, where coexistence of both is considered (69). Given this difficult situation, scintigraphy with gallium-67 has been proposed as a useful tool in differential diagnosis, through pancreas uptake, submandibular glands (especially if asymmetrical) in IgG4 disease, while in sarcoidosis it predominates in lacrimal glands,

supraclavicular, mediastinal adenopathies and muscle tissue (70).

Although this is not the purpose of this review, treatment varies from clinical observation in asymptomatic forms to a complete immunosuppressive treatment with alkylating agents in the most severe forms. Additionally, anti-TNF has been used as an alternative in refractory cases, which is logical due to the lytic effect of these on granulomas (71).

In conclusion, sarcoidosis is a multisystemic granulomatous disease difficult to identify. Its differential diagnosis is broad and requires a methodical discard process as there is no definitive diagnostic test. Finally, the treatment depends on the organ involvement degree and its chronicity.

CONFLICT OF INTEREST

None to be declared.

BIBLIOGRAPHIC REFERENCES

1. Spagnolo P, Luppi F, Roversi P, Cerri S, Fabbri LM, Richeldi L. Sarcoidosis: challenging diagnostic aspects of an old disease. Am J Med. 2012 Feb;125(2):118-25. DOI 10.1016/j.amjmed.2011.06.003.
2. Johns CJ, Michele TM. The clinical management of sarcoidosis. A 50-year experience at the Johns Hopkins Hospital. Medicine (Baltimore). 1999 Mar;78(2):65-111.
3. Hem E. [Multiple benign sarcoid of the skin--100 years since Caesar Boeck's pioneering article]. Tidsskr Nor Laegeforen. 1999 Dec;119(30):4567-9.
4. Iannuzzi MC, Fontana JR. Sarcoidosis: clinical presentation, immunopathogenesis, and therapeutics. JAMA. 2011 Jan 26;305(4):391-9. DOI 10.1001/jama.2011.10.

5. Westney GE, Judson MA. Racial and ethnic disparities in sarcoidosis: from genetics to socioeconomics. Clin Chest Med. 2006 Sep;27(3):453-62, vi.
6. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. N Engl J Med. 2007 Nov;357(21):2153-65.
7. Lynch JP 3rd, Hwang J, Bradfield J, Fishbein M, Shivkumar K, Tung R. Cardiac involvement in sarcoidosis: evolving concepts in diagnosis and treatment. Semin Respir Crit Care Med. 2014 Jun;35(3):372-90. DOI 10.1055/s-0034-1376889.
8. Santamaria-Alza Y, Fajardo Rivero JE. Sarcoidosis: a series of cases from the northeastern of Colombia. Neumol Cir Thorax. 2017 Jan-Mar;76(1):14-6.
9. 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. 2018 Feb. Pii: S1699- 258X(18)30021-4. DOI 10.1016/j.reuma.2018.01.001.
10. Judson MA, Baughman RP, Thompson BW, Teirstein AS, Terrin ML, Rossman MD, et al. Two year prognosis of sarcoidosis: the ACCESS experience. Sarcoidosis Vasc Diffuse Lung Dis. 2003 Oct;20(3):204-11.
11. Co DO, Hogan LH, Il-Kim S, Sandor M. T cell contributions to the different phases of granuloma formation. Immunol Lett. 2004 Mar;92(1-2):135-42.
12. Song Z, Marzilli L, Greenlee BM, Chen ES, Silver RF, Askin FB, et al. Mycobacterial catalase-peroxidase is a tissue antigen and target of the adaptive immune response in systemic sarcoidosis. J Exp Med. 2005 Mar;201(5):755-67. Erratum in: J Exp Med. 2005 Sep 5;202(5):721.
13. Baughman RP, Teirstein AS, Judson MA, Rossman MD, Yeager H Jr, Bresnitz EA, et al.Clinical characteristics of patients in a case control study of sarcoidosis. Am J

Respir Crit Care Med. 2001 Nov;164(10 Pt 1):1885-9.

14. Rybicki BA, Major M, Popovich J Jr, Maliarik MJ, Iannuzzi MC. Racial differences in sarcoidosis incidence: a 5-year study in a health maintenance organization. Am J Epidemiol. 1997 Feb;145(3):234-41.
15. Carmona EM, Kalra S, Ryu JH. Pulmonary Sarcoidosis: Diagnosis and Treatment. May Clin Proc. 2016 Jul;91(7):946-54. DOI 10.1016/j.mayocp.2016.03.004.
16. Hamzeh N. Sarcoidosis. Med Clin North Am. 2011 Nov;95(6):1223-34. DOI 10.1016/j.mcna.2011.08.004.
17. Chen ES, Moller DR. Etiology of sarcoidosis. Clin Chest Med. 2008 Sep;29(3):365-77, vii. DOI 10.1016/j.ccm.2008.03.011.
18. Haimovic A, Sanchez M, Judson MA, Prystowsky S. Sarcoidosis: a comprehensive review and update for the dermatologist: part I. Cutaneous disease. J Am Acad Dermatol. 2012 May;66(5):699.e1-18; quiz 717-8. DOI 10.1016/j.jaad.2011.11.965.
19. Govender P, Berman JS. The Diagnosis of Sarcoidosis. Clin Chest Med. 2015 Dec;36(4):585-602. DOI 10.1016/j.ccm.2015.08.003.
20. Chappity P, Kumar R, Sahoo AK. Heerfordt's Syndrome Presenting with Recurrent Facial Nerve Palsy: Case report and 10-year literature review. Sultan Qaboos Univ Med J. 2015 Feb;15(1):e124-8.
21. Baughman RP. Pulmonary sarcoidosis. Clin Chest Med. 2004 Sep;25(3):521-30, vi.
22. Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. Am J Respir Crit Care Med. 1999 Aug;160(2):736- 55.

23. Judson MA. The Clinical Features of Sarcoidosis: A Comprehensive Review. Clin Rev Allergy Immunol. 2015 Aug;49(1):63-78. DOI 10.1007/s12016-014-8450-y.
24. Hillerdal G, Nöu E, Osterman K, Schmekel B. Sarcoidosis: epidemiology and prognosis. A 15-year European study. Am Rev Respir Dis. 1984 Jul;130(1):29-32.
25. Siltzbach LE, James DG, Neville E, Turiaf J, Battesti JP, Sharma OP, et al. Course and prognosis of sarcoidosis around the world. Am J Med. 1974 Dec;57(6):847-52.
26. Lynch JP 3rd, Kazerooni EA, Gay SE. Pulmonary sarcoidosis. Clin Chest Med. 1997 Dec;18(4):755-85.
27. Baughman RP, Winget DB, Bowen EH, Lower EE. Predicting respiratory failure in sarcoidosis patients. Sarcoidosis Vasc Diffuse Lung Dis. 1997 Sep;14(2):154-8.
28. Nishimura K, Itoh H, Kitaichi M, Nagai S, Izumi T. CT and pathological correlation of pulmonary sarcoidosis. Semin Ultrasound CT MR. 1995 Oct;16(5):361-70.
29. Brauner MW, Grenier P, Mompoint D, Lenoir S, de Crémoux H. Pulmonary sarcoidosis: evaluation with high-resolution CT. Radiology. 1989 Aug;172(2):467-71.
30. Müller NL, Miller RR. Ground-glass attenuation, nodules, alveolitis, and sarcoid granulomas. Radiology. 1993 Oct;189(1):31-2.
31. Hamper UM, Fishman EK, Khouri NF, Johns CJ, Wang KP, Siegelman SS. Typical and atypical CT manifestations of pulmonary sarcoidosis. J Comput Assist Tomogr. 1986 Nov- Dec;10(6):928-36.
32. Reich JM. Mortality of intrathoracic sarcoidosis in referral vs population-based settings: influence of stage, ethnicity, and corticosteroid therapy. Chest. 2002 Jan;121(1):32-9.
33. Davies CW, Tasker AD, Padley SP, Davies RJ, Gleeson FV. Air trapping in

sarcoidosis on computed tomography: correlation with lung function. Clin Radiol. 2000 Mar;55(3):217- 21.

34. Bartz RR, Stern EJ. Airways obstruction in patients with sarcoidosis: expiratory CT scan findings. J Thorac Imaging. 2000 Oct;15(4):285-9.
35. Abehsera M, Valeyre D, Grenier P, Jaillet H, Battesti JP, Brauner MW. Sarcoidosis with pulmonary fibrosis: CT patterns and correlation with pulmonary function. AJR Am J Roentgenol. 2000 Jun;174(6):1751-7.
36. Jamilloux Y, Kodjikian L, Broussolle C, Sève P. Sarcoidosis and uveitis. Autoimmun Rev. 2014 Aug;13(8):840-9. DOI 10.1016/j.autrev.2014.04.001.
37. Martínez-Berriotxoa A, Fonollosa A, Artaraz J. [Uveitis: diagnostic approach]. Rev Clin Esp. 2012 Oct;212(9):442-52. DOI 10.1016/j.rce.2011.12.004.
38. 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.
39. Kansal V, Dollin M. Ocular involvement in sarcoidosis. CMAJ. 2017 Apr;189(16):E609. DOI 10.1503/cmaj.160569.
40. Zapata-González F, Vásquez-Ochoa LA, Arroyave-Sierra JE, Arredondo-Ossa MI, Molina-Vélez V, Río-Cobaleda D. Cutaneous sarcoidosis. CES Med. 2014 Jul-Dec;28(2):293-306.
41. Valovis R. Sarcoidosis clinical study of 51 cases and review of the literature. Colombian Medical Act. 1977;2(2):101-10.
42. Visser H, Vos K, Zanelli E, Verduyn W, Schreuder GM, Speyer I, et al. Sarcoid arthritis: clinical characteristics, diagnostic aspects, and risk factors. Ann Rheum Dis. 2002 Jun;61(6):499-504.
43. Banse C, Goëb V. Do not forget the joint involvement of sarcoidosis.

Immunotherapy. 2015;7(6):599-600. DOI 10.2217/imt.15.24.

44. Kidd DP. Sarcoidosis of the central nervous system: clinical features, imaging, and CSF results. J Neurol. 2018 Aug;265(8):1906-15. DOI 10.1007/s00415-018-8928-2.
45. Rocha ÓG, García PK, Echeverri JE, D'Achiardi RE, Rodríguez MP, Córdoba JP, et al. Sarcoidosis and renal involvement: report of a case and review of the scientific literature. University of Medellin. 2012 Jan-Mar;53(1):94-106.
46. Holmes J, Lazarus A. Sarcoidosis: extrathoracic manifestations. Dis Mon. 2009 Nov;55(11):675-92. DOI 10.1016/j.disamonth.2009.05.002.
47. Okumus G, Musellim B, Cetinkaya E, Turker H, Uzaslan E, Yenturk E, et al. Extrapulmonary involvement in patients with sarcoidosis in Turkey. Respirology. 2011 Apr;16(3):446-50. DOI 10.1111/j.1440-1843.2010.01878.x.
48. 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 Jun;35(3):336-51. DOI 10.1055/s-0034-1381229.
49. Bonfioli AA, Orefice F. Sarcoidosis. Semin Ophthalmol. 2005 Jul-Sep;20(3):177-82.
50. Harvey J, Catoggio L, Gallagher PJ, Maddison PJ. Salivary gland biopsy in sarcoidosis. Sarcoidosis. 1989 Mar;6(1):47-50.
51. Blaise P, Fardeau C, Chapelon C, Bodaghi B, Le Hoang P. Minor salivary gland biopsy in diagnosing ocular sarcoidosis. Br J Ophthalmol. 2011 Dec;95(12):1731-4. DOI 10.1136/bjophthalmol-2011-300129.
52. Truedson H, Stjernberg N, Thunell M. Scalene lymph node biopsy. A diagnostic method in sarcoidosis. Acta Chir Scand. 1985;151(2):121-3.
53. Karagiannidis A, Karavalaki M, Koulaouzidis A. Hepatic sarcoidosis. Ann Hepatol.

2006 Oct-Dec;5(4):251-6.

54. Ungprasert P, Carmona EM, Crowson CS, Matteson EL. Diagnostic Utility of Angiotensin-Converting Enzyme in Sarcoidosis: A Population-Based Study. Lung. 2016 Feb;194(1):91-5. DOI 10.1007/s00408-015-9826-3.
55. Lieberman J. Elevation of serum Angiotensin-Converting-Enzyme (ACE) level in sarcoidosis. Am J Med. 1975 Sep;59(3):365-72.
56. Stouten K, van de Werken M, Tchetverikov I, Saboerali M, Vermeer HJ, Castel R, et al. Extreme elevation of serum angiotensin-converting enzyme (ACE) activity: always consider familial ACE hyperactivity. Ann Clin Biochem. 2014 Mar;51(Pt 2):289-93. DOI 10.1177/0004563213489812.
57. Studdy PR, Bird R. Serum angiotensin converting enzyme in sarcoidosis—its value in present clinical practice. Ann Clin Biochem. 1989 Jan;26 (Pt 1):13-8.
58. Gupta D, Chetty M, Kumar N, Aggarwal AN, Jindal SK. Anergy to tuberculin in sarcoidosis is not influenced by high prevalence of tuberculin sensitivity in the population. Sarcoidosis Vasc Diffuse Lung Dis. 2003 Mar;20(1):40-5.
59. Siltzbach LE. The Kveim test in sarcoidosis. A study of 750 patients. JAMA. 1961 Nov;178:476-82.
60. Sulavik SB, Spencer RP, Palestro CJ, Swyer AJ, Teirstein AS, Goldsmith SJ. Specificity and sensitivity of distinctive chest radiographic and/or 67Ga images in the noninvasive diagnosis of sarcoidosis. Chest. 1993 Feb;103(2):403-9.
61. 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 Diffuse Lung Dis. 2014 Apr;31(1):19-27.
62. Bickett AN, Lower EE, Baughman RP. Sarcoidosis Diagnostic Score: A Systematic

Evaluation to Enhance the Diagnosis of Sarcoidosis. Chest. 2018 Nov;154(5):1052-60. DOI 10.1016/j.chest.2018.05.003.

63. Newman LS, Rose CS, Maier LA. Sarcoidosis. N Engl J Med. 1997 Apr;336(17):1224-34. Erratum in: N Engl J Med 1997 Jul;337(2):139.
64. Judson MA. The diagnosis of sarcoidosis. Clin Chest Med. 2008 Sep;29(3):415-27, viii. DOI 10.1016/j.ccm.2008.03.009.
65. Verbsky JW, Routes JM. Sarcoidosis and common variable immunodeficiency: similarities and differences. Semin Respir Crit Care Med. 2014 Jun;35(3):330-5. DOI 10.1055/s-0034-1376862.
66. Ramos-Casals M, Brito-Zerón P, García-Carrasco M, Font J. Sarcoidosis or Sjögren syndrome? Clues to defining mimicry or coexistence in 59 cases. Medicine (Baltimore). 2004 Mar;83(2):85-95.
67. Yu JQ, Doss M, Codreanu I, Zhuang H. PET/CT in Patients with Sarcoidosis or IgG4 Disease. PET Clin. 2012 Apr;7(2):191-210. DOI 10.1016/j.cpet.2012.01.005.
68. Yu J, Hall T, Kale S, Phillips A, Madge S. IgG4 disease: a revised diagnosis of sarcoidosis after 36 years of treatment. Br J Hosp Med (Lond). 2013 Aug;74(8):470-1.
69. Michel L, Clairand R, Néel A, Masseau A, Frampas E, Hamidou M. Association of IgG4- related disease and sarcoidosis. Thorax. 2011 Oct;66(10):920-1. DOI 10.1136/thx.2011.160341.
70. Ishii S, Miyajima M, Sakuma K, Kikuchi K, Shishido F. Comparison between sarcoidosis and IgG4-related disease by whole-body 67Ga scintigraphy. Nucl Med Commun. 2013 Jan;34(1):13-8.DOI 10.1097/MNM.0b013e32835a2eea.
71. Baughman RP, Grutters JC. New treatment strategies for pulmonary sarcoidosis:

antimetabolites, biological drugs, and other treatment approaches. Lancet Respir Med. 2015 Oct;3(10):813-22. DOI 10.1016/S2213-2600(15)00199-X.