Sarcoidosis

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KEYWORDS

• Sarcoidosis • Diagnosis • Clinical manifestations • Treatment • Management

KEY POINTS

- Sarcoidosis is a systemic granulomatous disorder of unknown cause that results from a complex interplay between infectious/environmental triggers and genetic factors leading to an aberrant immune response.
- There is no diagnostic gold standard and the diagnosis is most likely in the presence of compatible clinical and radiological features coupled with evidence of noncaseating granulomatous inflammation at disease sites and after exclusion of other diseases that may present similarly.
- The majority of patients have a remitting disease with or without treatment. However, about one-third of the patients develop chronic disease, with extrapulmonary manifestations representing a major cause of morbidity and mortality.
- Corticosteroids are the mainstay of treatment but they do not cure the disease and are associated with significant side effects.
- Patients with refractory or life/organ-threatening diseases should be referred to expert centers.

INTRODUCTION

Sarcoidosis is a highly variable and unpredictable systemic disorder characterized by granulomatous inflammation in affected organs. Disease pathogenesis involves a complex interplay between a putative triggering antigen (or antigens), which remains unknown, and the host's genetic makeup. The incidence, severity, and clinical manifestations of sarcoidosis highly depend on race and ethnicity. Indeed, African Americans are afflicted more often and more severely than Caucasians, although prediction of disease behavior is difficult. The complex multidimensional nature of sarcoidosis coupled with its wide range of clinical manifestations underscores the need for a multidisciplinary approach to patient care.

EPIDEMIOLOGY

Sarcoidosis occurs worldwide with an overall prevalence ranging between 50 and 160 per 100,000 population.[1] Although traditionally regarded as a disease of young people,

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recent data shows that more than half of the patients are older than 40 years at diagnosis.[2] The disease affects both sexes with a slight predilection for women, particularly among African Americans. Sarcoidosis is more common in Black Americans than in White Americans, with an estimated lifetime disease risk of 2.4% and 0.85%, respectively.[3] Northern Europeans are another ethnic group at particularly high risk for the disease, with a prevalence as high as 160 per 100,000 in Sweden.[4] Disease presentation and patterns of organ involvement differ substantially across ethnicities. Indeed, sarcoidosis tends to affect black people more acutely and more severely than people of other races.[3,5] In addition, some extra-thoracic manifestations are more prevalent in certain populations, such as chronic uveitis in African Americans and Japanese, lupus pernio in African Americans, and erythema nodosum in Scandinavians.[5] The observation that the prevalence of sarcoidosis follows a rough north–south gradient along with seasonal clustering of cases in winter and early spring suggests that sarcoidosis results from a complex (and poorly understood) interaction between environmental and genetic factors.[5,6] Finally, a lower disease prevalence in smokers has been reported but the evidence is inconsistent.

PATHOLOGY, PATHOGENESIS, AND POTENTIAL ETIOLOGIC FACTORS

Histopathology

Nonnecrotizing granulomas, the histopathological hallmark of sarcoidosis, are discrete aggregates of chronic inflammatory cells (ie, macrophages, epithelioid cells, multinucleated giant cells, and $CD4^+$ T lymphocytes), which tend to merge to form nodules in the mm size range.[7] Sarcoid granulomas are "epithelioid cell granulomas," as the epithelioid cells, which derive from mononuclear phagocytes (ie, monocytes and macrophages), are the dominant cell type.[7] They are located at the center of the granuloma surrounded by a mantle of lymphocytes, tissue macrophages, and giant cells, which also derive from mononuclear phagocytes. The granuloma is surrounded by fibroblasts and lamellar rings of hyaline collagen.

According to the general paradigm of disease immunopathogenesis, sarcoid granulomas result from a T-cell-mediated response to an (yet unknown) antigen that is processed by antigen-presenting cells—such as macrophages or dendritic cells—and presented to antigen-specific $CD4^+$ T cells in the context of class I or class II Human Leukocyte Antigen (HLA) molecules.[8] Specifically, the antigenic peptide and the HLA class II molecule activate antigen-specific $CD4^+$ T cells by binding to the T-cell receptor (TCR) on the T-cell surface. Once activated, the $CD4^+$ T cells orchestrate the immune response that culminates with granuloma formation.[8] A multitude of cytokines are involved in this process, including interleukin (IL)-2, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ, which amplify the immune response by triggering macrophages to secrete, among others, TNF-α, IL-1, IL-6, IL-8, IL-12, IL-15, and IL-18.[9] In sarcoidosis, granulomatous inflammation is a highly polarized Th1 type cytokine response. However, in cases evolving from granulomatous inflammation to fibrosis, a shift from a Th1- to a Th2-type cytokine pattern is likely to occur.[9–11]

Genetic Factors

Several lines of evidence support a major role of host susceptibility in the pathogenesis of sarcoidosis. They include the familial occurrence of the disease, with a pooled prevalence as high as 7.3% in a meta-analysis based on 12 populations,[12] ethnic variations in its epidemiology and clinical manifestations as well as genetic studies showing consistent associations between a variety of variants, mostly within the HLA region, and sarcoidosis susceptibility, phenotypes, and prognosis.[13] However,

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subsets of patients sharing the same HLA associations may display different clinical manifestations based on their ethnic and racial background, suggesting that multiple factors are involved in the phenotypic expressions of sarcoidosis. Nevertheless, the *HLA*-DRB1*1101 allele is a risk factor for sarcoidosis in both Caucasians and African Americans,[14] whereas Löfgren's syndrome is strongly associated with the HLA-DRB1*0301 allele, particularly in Scandinavians.[15,16] Additional variants that confer susceptibility to sarcoidosis are located within butyrophilin-like 2 (*BTNL2*)[17] and annexin A11 (*ANXA11*)[18] genes.

Potential Etiologies

Numerous microorganisms have been implicated as possible causes of sarcoidosis.[19] Several studies have explored the etiological role of *Mycobacterium tuberculosis* based on the histologic similarities between sarcoidosis and mycobacterial infection.[20,21] Song and colleagues[22] identified *M tuberculosis* catalase-peroxidase (*mKatG*), a mycobacterial antigen, in 5 of 9 sarcoidosis tissues but in none of 14 control tissues. Moreover, T cells reactive to *mKatG* were found at increased levels in both peripheral blood and bronchoalveolar lavage (BAL) fluid from sarcoidosis patients compared with healthy controls.[21] *Propionibacterium acnes* and *P granulosum* have also been isolated in a significantly higher proportion of sarcoidosis specimens compared with control specimens.[19] Although the infectious theory is intriguing, a definitive conclusion as to whether microorganisms play a role in the pathogenesis of sarcoidosis will require more extensive investigations. Certain occupational exposures, most notably beryllium, can induce sarcoid-like granulomatous inflammation,[23] thus suggesting that occupational or environmental agents might also trigger the disease, at least in a subset of cases. In this regard, firefighters exposed to World Trade Center (WTC) "dust" were at significantly increased risk of developing sarcoidosis-like pulmonary disease during the 5 years following the disaster.[24]

DIAGNOSTIC APPROACH

There is no diagnostic gold standard for sarcoidosis. However, the diagnosis is highly probable in the presence of compatible clinical-radiological features supported by histologic evidence of non-necrotizing granulomas in one or more affected tissues and after the exclusion of alternative causes of granulomatous inflammation.[25] Yet, there are scenarios in which a confident diagnosis of sarcoidosis can be made without histologic confirmation, such as patients presenting with Löfgren's syndrome (ie, bilateral hilar lymph adenopathy [BHL], fever, erythema nodosum, and arthralgia), Heerfordt's syndrome (ie, facial nerve paralysis, parotid or salivary glands enlargement and anterior uveitis), lupus pernio (ie, indurated purplish papules or plaques that involve the nose, cheeks, lips, ears, and eyelids) as well as in asymptomatic individuals presenting with symmetric BHL.[5,6,25] In this latter case, however a close clinical follow-up to ensure stability or resolution is recommended.[25] Biopsies should be obtained from the most accessible affected sites such as the skin, or palpable lymph nodes. If none of these sites is affected, the next step is sampling intrathoracic lymph nodes or the lung parenchyma. Serum levels of angiotensin-converting enzyme (ACE) are increased in up to 75% of untreated patients with sarcoidosis. However, its poor sensitivity and insufficient specificity make it ACE of limited value as a diagnostic tool.[26]

BAL supports the diagnosis of sarcoidosis when it shows a moderate (20% to 50%) lymphocytosis with a T lymphocyte CD4:CD8 ratio greater than 3.5.[26,27] BAL is also useful in excluding alternative diagnoses such as infections and malignancy.

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Endobronchial mucosal biopsy reveals non-necrotizing granulomas in about 70% of cases in the presence of visible abnormalities (ie, cobblestone appearance of the mucosa) as well as in around 30% of cases with a normal-appearing mucosa. Transbronchial lung biopsy has a diagnostic yield of 50% to 75% in patients with BHL or compatible parenchymal abnormalities on chest high-resolution computed tomography (HRCT) (ie, micronodules with a perilymphatic distribution clustered along the bronchovascular bundles, interlobular septa, and interlobar fissures).[11] Alternatively, transbronchial needle aspiration (TBNA) with or without ultrasound guidance can be used to sample mediastinal lymph nodes or pulmonary lesions. Notably, in patients with mediastinal lymphadenopathy and a clinical suspicion of sarcoidosis, endoscopic ultrasound-guided needle aspiration of intrathoracic lymph nodes via esophageal endoscopic ultrasound (EUS) or endobronchial ultrasound (EBUS) has a diagnostic yield of 80% to 90%.[28] If diagnostic uncertainty persists, mediastinal lymph node biopsy via mediastinoscopy is the preferred diagnostic modality. Lung biopsy via thoracoscopy is rarely needed.

CLINICAL MANIFESTATIONS

The spectrum of clinical manifestations of sarcoidosis is highly heterogeneous. Although pulmonary involvement is almost universal, any organ can be affected. The presenting symptoms are generally related to the organs involved, but patients may also present with nonspecific systemic symptoms, such as low-grade fever, weight loss, and fatigue.

Respiratory Tract

Sarcoidosis affects the lungs and mediastinal lymph nodes in more than 90% of cases.[5,6,25] Accordingly, the main respiratory complaints are cough, shortness of breath, and chest pain. However, 30% to 60% of patients with pulmonary disease are asymptomatic, and are diagnosed incidentally.[25] BHL is the most common radiographic presentation, and when accompanied by erythema nodosum and arthralgia, defines Löfgren syndrome, an acute, self-limiting, and genetically distinct form of the disease.[9,13,16,29] Historically, pulmonary involvement has been classified using the Scadding system, which, by relying on chest radiograph, provides a rough estimate of the likelihood of resolution at 5 years[30] (**Figs. 1–4**). The Scadding system is simple and reproducible, but does not correlate with the likelihood of cutaneous or ocular disease and correlates only poorly with lung function tests and need for treatment in individual patients. HRCT is generally performed to evaluate abnormalities seen on chest radiograph and typically reveals hilar and mediastinal lymphadenopathy, bronchovascular bundle thickening, nodules with a perilymphatic distribution (ie, along bronchi, vessels, and subpleural regions), and ground glass opacity[11,31,32] (**Fig. 5**). Pulmonary fibrosis, which develops in about 20% of cases, predominates in the middle and upper zones and manifests as masses, cysts, distortion of the airways and lung parenchyma, and traction bronchiectasis[11,31,32] (**Fig. 6**). Fluorine-18-fluorodeoxyglucose-positron emission tomography (FDG-PET) may be helpful in identifying occult lesions more accessible to biopsy, but does not differentiate sarcoidosis from other inflammatory conditions, infection, or malignancy. When abnormal, pulmonary function tests (PFTs) generally reveal a restrictive ventilatory defect associated with a reduced diffusing capacity of the lung for carbon monoxide (DL_{CO}) whereas distortion of the airways and endobronchial disease may lead to an obstructive pattern.[33] PFTs may also allow to assess the severity of respiratory impairment and to monitor the disease course.[33]

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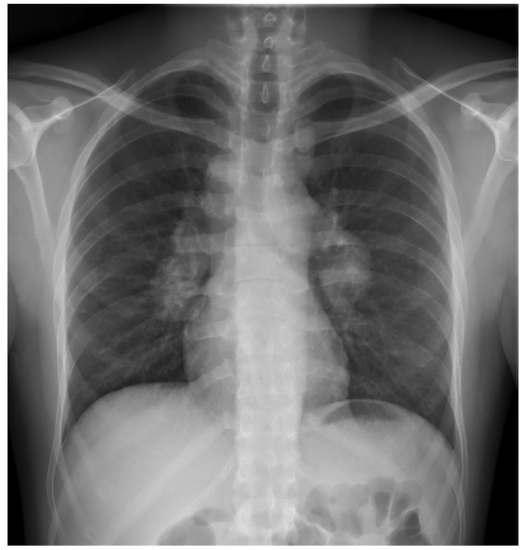

Fig. 1. Scadding stage I: bilateral hilar lymphadenopathy.

EXTRAPULMONARY MANIFESTATIONS

Extrapulmonary involvement is seen in up to 50% of sarcoidosis patients,[34] with isolated extrapulmonary disease occurring in less than 10% of total cases.[35] Such cases generally represent a diagnostic dilemma. The most common sites of disease outside the lung are skin, peripheral lymph nodes, eyes, and liver.[36]

Skin

The most common cutaneous manifestation of sarcoidosis is erythema nodosum (EN), a form of panniculitis characterized by painful lesions on the anterior surface of the

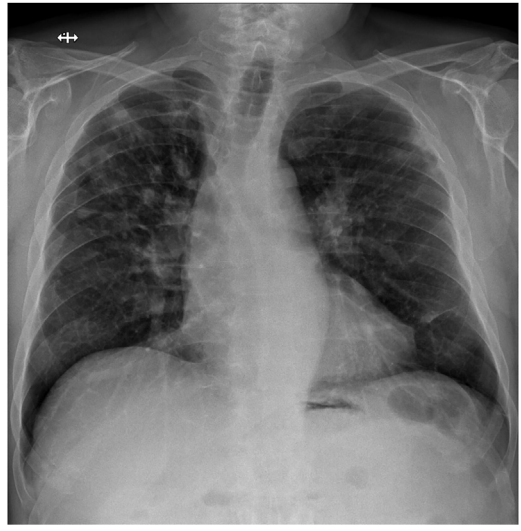

Fig. 2. Scadding stage II: bilateral hilar lymphadenopathy and parenchymal infiltrates.

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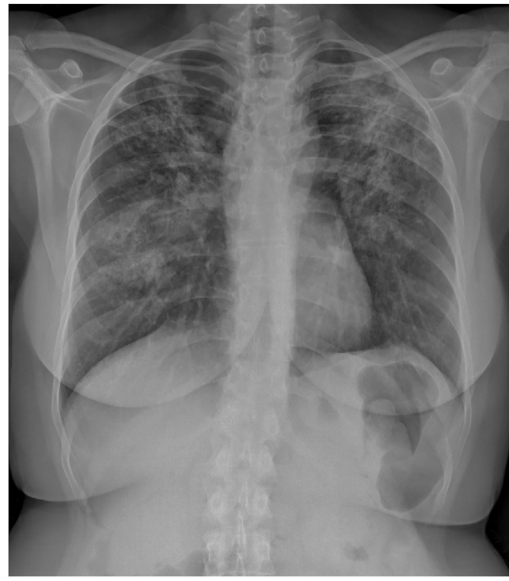

Fig. 3. Scadding stage III: isolated parenchymal infiltrates.

lower limbs. EN occurs in approximately 25% of cases and is typically associated with Löfgren's syndrome.[29,37] Notably, EN should not be biopsied, as it does not contain granulomas. Several types of skin lesions can occur, including diffuse erythematous papules, subcutaneous nodules, and plaques.[38] Lupus pernio, the most characteristic cutaneous manifestation of sarcoidosis, is characterized by red-to-purple indurated plaques, papules, or nodules that primarily affect the nose, cheeks, and ears. Early recognition and treatment are paramount, as lupus pernio can infiltrate the underlying tissues and cause disfigurement. Typically, skin sarcoidosis involves scars and tattoos.[37,38]

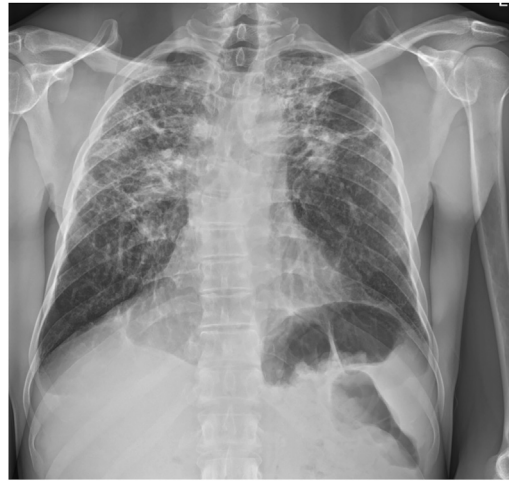

Fig. 4. Scadding stage IV: pulmonary fibrosis.

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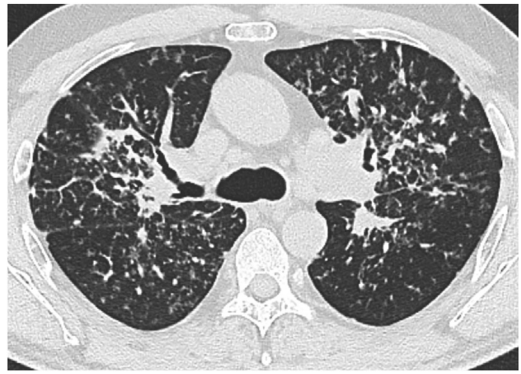

Fig. 5. Chest CT showing diffuse micronodules prevalent in the upper zones and with a typical peribronchovascular distribution. This pattern is typical, though not pathognomonic, of sarcoidosis.

Eyes

Ocular involvement occurs in 10% to 50% of sarcoidosis patients and is the presenting manifestation in about 5% of cases.[39] The prevalence is higher in females as well as in African American and Japanese patients.[40] Any part of the eye can be involved, although the anterior and posterior ocular segments, conjunctiva, and lacrimal glands are mostly commonly affected. Uveitis is the most common form of ocular sarcoidosis, with anterior uveitis (defined as iritis and/or iridocyclitis) accounting for up to 75% of all sarcoid uveitis cases.[40] Symptoms include blurry vision, redness, photophobia, dry

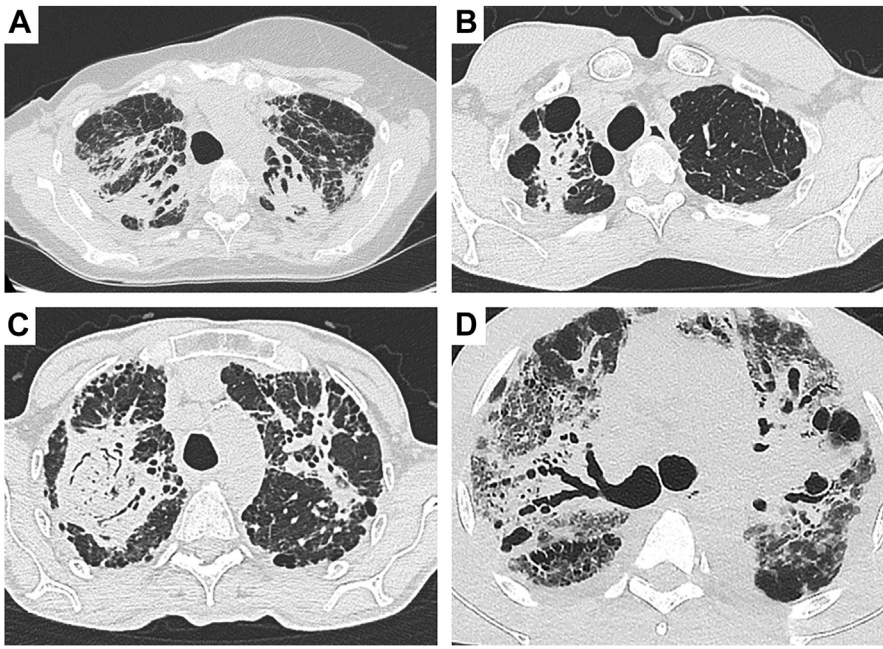

Fig. 6. Advanced fibrotic disease (*A–D*) characterized by distortion of the airways (*D*) and lung parenchyma (*A*); fibrocystic disease (*B*); pulmonary fibrosis colonized by *Aspergillum fumigatus* (*C*).

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eyes, and ocular pain, whereas posterior or intermediate uveitis generally causes floaters. As ocular involvement can be asymptomatic, all patients with newly diagnosed sarcoidosis should undergo ophthalmologic screening. Refractory and sight-threatening forms require a multi-disciplinary approach and aggressive treatment.

Heart

Cardiac sarcoidosis (CS) is clinically evident in about 5% of patients, although the prevalence of subclinical involvement is significantly higher (20% to 70%), as suggested by autopsy and cardiac imaging studies.[41] Similarly, CS can be benign and discovered incidentally or cause sudden death due to ventricular tachyarrhythmia or bradyarrhythmia.[41] Of note, cardiac disease accounts for as many as 85% of deaths among Japanese patients with sarcoidosis.[42] Heart block and arrhythmias (due to involvement of the conducting system) are the most common manifestations of CS.[43] Cardiac Magnetic Resonance (CMR) and/or FDG-PET are generally used to confirm the diagnosis of CS, as endomyocardial biopsy has a low sensitivity due to the patchy distribution of the disease and exposes patients to risks.[44] No single tool can reliably detect early and asymptomatic disease and the best approach remains clinical suspicion of cardiac involvement.

Nervous system

Historically, neurosarcoidosis (NS) has been reported to occur in 5% to 10% of all sarcoidosis patients, although these prevalence rates derive from pulmonary sarcoidosis-focused cohorts. Indeed, autopsy studies have identified clinically occult NS in as many as 34% of patients with systemic sarcoidosis.[45] Notably, only about 30% of patients with NS have systemic manifestations of the disease at presentation, with the vast majority of them eventually developing systemic disease, whereas in 10% to 20% of case NS remains isolated.[46] Any part of the nervous system can be involved but the cranial nerves, hypothalamus, meninges, spinal cord, and peripheral nerves are most commonly affected.[47] Optic neuritis and optic neuropathy caused by infiltrating or mass-like lesions may also occur. The diagnosis—which is particularly challenging when NS occurs in isolation—is usually straightforward when neurologic symptoms develop in patients with an established diagnosis of sarcoidosis.

Liver, spleen, and kidney

Hepatic sarcoidosis has been reported in up to 70% of patients and is twice as common in African Americans as in Caucasians. Most cases are asymptomatic, but many have liver function test abnormalities or hepatomegaly.[48] Portal hypertension and cirrhosis are a rare complication of long-standing hepatic disease.[49] Splenic involvement is also common in patients with sarcoidosis, although most cases are asymptomatic.[50] Splenomegaly is usually homogeneous, but multiple low-attenuating nodular lesions indistinguishable from a metastatic disease may also be seen. Renal involvement is a rare but potentially serious complication of sarcoidosis. It ranges from disordered calcium homeostasis leading to hypercalcemia and hypercalciuria, the most common manifestations, to tubulointerstitial nephritis.[51] Severe hypercalcemia and/or hypercalciuria are indications for treatment, as they may lead to renal failure.

SYSTEMIC MANIFESTATIONS

Fatigue, is the most common systemic symptom of sarcoidosis being reported in up to 80% of patients,[52] with fever, sleep disorders, irritability, weight loss, anorexia, and

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flushing representing additional common complaints. Small fiber neuropathy (SFN) is another common complication of sarcoidosis that manifests as numbness, pain, and migratory and intermittent paraesthesia.[53] In a study, burning pain was the most severe and disabling symptom and was present in about one-third of patients.[54] SFN is more common in Caucasians and in women, and is often refractory to standard therapies used for systemic disease.[55]

TREATMENT

In sarcoidosis, a "wait and watch strategy" is often justified, as the disease frequently remits with or without therapy. In addition, corticosteroids, the cornerstone of treatment, do not cure the disease and are associated with serious side effects. Therefore, treatment is indicated in patients with progressive and organ/life-threatening disease or significantly impaired quality of life, weighed carefully the pros and cons of initiating therapy.[56]

Pulmonary sarcoidosis

Most patients with pulmonary sarcoidosis do not require systemic therapy.[56,57] When treatment is needed, corticosteroids are the first-line agents, although the recommendation for their use is based on low-quality evidence.[56] The 2021 guideline document on treatment recommends corticosteroid treatment for patients at high risk of mortality or permanent disability to improve and/or preserve FVC and quality of life.[56] Specific indications for treatment include bothersome or worsening pulmonary symptoms (ie, cough, dyspnea, and chest pain), worsening lung function, or progression of radiographic abnormalities.[56] The optimal dose and duration of corticosteroid treatment are unknown, but most authors use an initial dose equivalent to prednisone 20 to 40 mg/daily continued for four to 6 weeks then slowly tapered and weaned over 9 to 12 months. For patients experiencing disease progression despite treatment or intolerable side effects of corticosteroids, escalation to immunosuppressive agents is suggested, with methotrexate being the preferred second-line agent ("Conditional recommendation, very low quality of evidence").[56] Less commonly used second-line drugs include azathioprine, leflunomide, hydroxychloroquine, and mycophenolate mofetil.[56] Patients with persistently active/progressive disease despite immunosuppressive therapy may respond to TNF-α antagonists (ie, infliximab or adalimumab), but their use is associated with an increased risk of infection.[56,58] Patients with end-stage pulmonary disease should be considered for lung transplantation.[59]

Skin sarcoidosis

Erythema nodosum is generally self-limiting and does not require specific therapy; however, short-course corticosteroids or nonsteroidal anti-inflammatory drugs may be needed to alleviate pain and discomfort. Systemic corticosteroids are generally reserved for patients with disfiguring or cosmetically distressing lesions, rapidly progressive disease, or following failure of local treatment.[37] Patients with refractory disease may benefit from a second-line agent, such as hydroxychloroquine or methotrexate, whereas in patients with active skin disease despite corticosteroids and/or immunosuppressive therapy the addition of infliximab should be considered.[56]

Ocular sarcoidosis

Owing to the risk of sight-threatening sequelae, ocular sarcoidosis almost invariably requires treatment, which generally starts with local corticosteroids.[60] Systemic

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corticosteroid treatment is required if local therapy fails to induce remission, whereas in patients who fail to respond to or do not tolerate corticosteroids escalation to second-line agents, mainly methotrexate, should be considered. Similar to pulmonary sarcoidosis, biologic agents are reserved for patients with recalcitrant disease.[56]

Cardiac sarcoidosis

The treatment of clinically overt CS consists of both suppression of cardiac inflammation—with the aim of preventing irreversible organ damage or conduction abnormalities—and appropriate care of arrhythmia and heart failure. Treatment is invariably required, as spontaneous remission does not occur.[61] Corticosteroids are the first-line treatment; prednisone (or equivalent) is generally initiated at a daily dose of 40 to 60 mg with a taper regimen similar to that for pulmonary sarcoidosis.[61] If corticosteroids fail to induce remission or are associated with an intolerable side effect, methotrexate is the preferred second-line agent,[13] whereas infliximab is reserved to refractory or progressive disease.[56] The anti-CD20 rituximab is a potential alternative to infliximab.[62] The standard indications for a permanent pacemaker or for an implantable cardioverter defibrillator apply also to CS. Heart transplantation is the definitive treatment for patients with refractory ventricular arrhythmias or end-stage heart failure.[63]

Neurosarcoidosis

NS almost invariably requires treatment, as spontaneous remission is rare. High-dose corticosteroids (equivalent to 1 mg/kg/d of prednisone) are the first-line treatment,[64] but severe manifestations, such as visual loss or altered mental status, or rapidly progressive disease may require intravenous methylprednisolone at a dose of 1 g per day for 3 to 5 days.[64,65] Methotrexate is the most commonly used second-line agents, but some experts suggest the early association of methotrexate to corticosteroids to prevent symptoms recurrence, as corticosteroids are gradually tapered.[64] As with pulmonary and extrapulmonary sarcoidosis, refractory disease requires biological treatment (ie, infliximab)[66] due to potentially catastrophic consequences of progressive disease. SFN generally responds poorly to standard therapy whereas intravenous immunoglobulin and biological agents appear to be more efficacious treatment options.[54]

FOLLOW-UP AND PROGNOSIS

The optimal modality of follow-up of patients with sarcoidosis has not been established. Most experts monitor symptoms, lung function, and imaging at 3 to 6 month intervals, but asymptomatic patients are evaluated less frequently. The clinical course of sarcoidosis is highly variable and unpredictable. However, in approximately half of the patients the disease resolves spontaneously within 2 to 3 years, whereas chronic disease (ie, disease lasting for $\geq$3 years) carries an increased risk of pulmonary and extrapulmonary fibrosis and impaired quality of life.[67] Patients with sarcoidosis have a lower survival compared with the general population,[68] with pulmonary fibrosis being the most common cause of death in western countries, whereas cardiac involvement is the main cause of mortality in Japan.[5,6]

SUMMARY

Sarcoidosis remains an enigmatic disease without a diagnostic gold standard, effective treatments, and reliable predictors of disease behavior. The disease is generally

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benign but a large minority of patients experience chronic progressive disease. Such diversity makes it difficult to classify patients into homogeneous subgroups, which contributes to the paucity of clinical trials of novel treatments. Patients with sarcoidosis of the heart, brain, and eyes and those with advanced and progressive/refractory disease should be referred to expert centers.

CLINICS CARE POINTS

- With very rare exceptions, the diagnosis of sarcoidosis should always be histologically confirmed.
- In the presence of noncaseating granuloma on biopsy, mycobacterial and fungal infection, foreign body reaction, and drug toxicity, among others, should be excluded.
- The easily accessible skin lesions and superficial lymph nodes should be the preferred sites for a biopsy.
- Elevation of serum angiotensin-converting enzyme level has a low sensitivity and poor specificity for sarcoidosis and should not be used as diagnostic tool.
- In patients with pulmonary sarcoidosis always look for extrapulmonary localizations of the disease.
- All patients diagnosed with sarcoidosis should be screened for cardiac involvement using clinical history, physical examination, and 12-lead electrocardiogram, as cardiac sarcoidosis can be life-threatening.
- The main indications for treatment are progressive granulomatous inflammation leading to life- or organ-threatening disease and disabling symptoms causing severe impairment of quality of life
- Second-line agents (ie, methotrexate) should be considered for cases of corticosteroid
- Failure, intolerance, or dependence.
- Consider biological agents (ie, infliximab) in refractory disease.

DISCLOSURE

P. Spagnolo reports personal fees from Novartis, Behring and Chiesi outside the submitted work. N. Bernardinello has nothing to disclose.

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