Contemporary optimized practice in the management of pulmonary sarcoidosis

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***Abstract*:** Pulmonary sarcoidosis is the most common form of sarcoidosis, accounting for the initial presentation in over 70% patients and with eventual presence in 90% of patients with sarcoidosis. However, the course of the disease is often unpredictable; its manifestations can be highly variable and its treatment may not be effective in all patients. As such, the optimized treatment of pulmonary sarcoidosis often requires a thoughtful personalized approach with the need to get the patient involved in decisions of management. In many patients with pulmonary sarcoidosis, the disease is self-limited and nonprogressive, thus treatment is not necessary. In other patients, the presence of significant symptoms or functional limitation often associated with worsening radiological changes and pulmonary function tests warrants treatment. Corticosteroids are the first-line treatment for pulmonary sarcoidosis; antimetabolites are second-line agents, with methotrexate being most commonly employed. Antitumor necrosis alpha antibodies, especially infliximab, are emerging as potential third-line agents. A high index of suspicion should be held for pulmonary hypertension and other comorbidities that may complicate the course of patients with advanced sarcoidosis. Lung transplantation may be the only option for patients who have refractory disease despite maximal medical therapy.

Keywords: pulmonary sarcoidosis, corticosteroids, methotrexate, infliximab, pulmonary hypertension, lung transplantation

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Introduction

Sarcoidosis is a granulomatous disease of unknown etiology that can affect virtually any organ in the body but most commonly manifests in the lungs.[1] Although its prevalence has been estimated at 10–20 per 100,000 of population, it varies in incidence among geographical regions as well in different races.[2] There are several manifestations of pulmonary sarcoidosis and clinical presentation can therefore be highly variable. The diagnosis of sarcoidosis is based on a biopsy demonstrating noncaseating granulomas with the exclusion of infectious, environmental, and malignant causes.[3] A large number of patients are asymptomatic and have nonprogressive disease or may have spontaneous remission so treatment is not always necessary although close observation is warranted. Progressive lung disease occurs in approximately a quarter of patients and disabling organ failure in about one-tenths of patients.[4] Therapy is invariably initiated in patients with significant symptoms, worsening radiographic changes, or declining pulmonary function tests. It is typically in the form of systemic steroids, but if there is a suboptimal response or inability to tolerate steroids, several alternative immunosuppressant medications exist.[5] There is no single optimal parameter to assess response to therapy and a combination of clinical and radiological data as well as pulmonary function tests are relied upon for ongoing management. Moreover, evaluation and management of pulmonary vascular and infectious complications is equally important as is the evaluation of extrapulmonary disease.[6] In this review, we will explore contemporary therapies for pulmonary sarcoidosis and discuss how they may be used to optimize the management of this condition.

Pathogenesis of pulmonary sarcoidosis

Sarcoidosis is a multisystem disorder characterized by the pathologic hallmark of granuloma formation in affected tissues.[7] Despite extensive

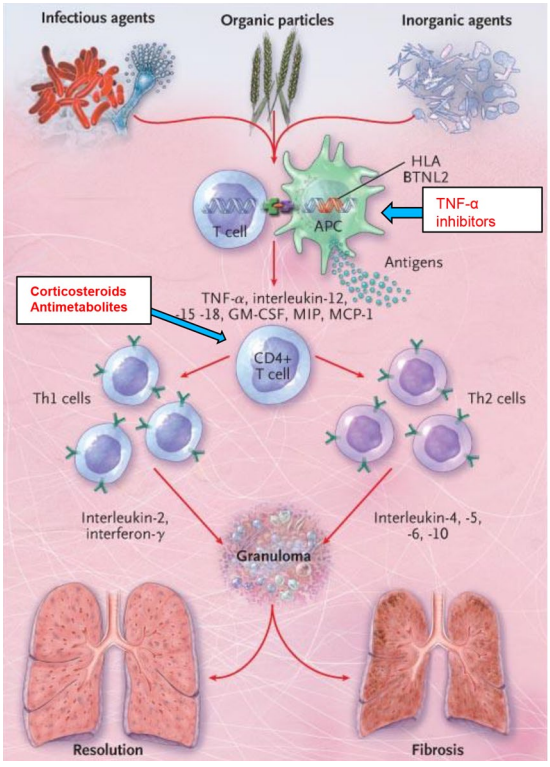

Figure 1. Hypothesized immunopathogenesis of sarcoidosis. Infectious, organic, and inorganic agents are possible antigens in sarcoidosis. Any causative microbe, if present, is probably cleared, leaving behind an undegradable product or initiating a cross-reacting immune response to self-antigen. Antigen-presenting cells (APC), in addition to producing high levels of tumor necrosis factor alpha (TNF-α), secrete interleukin-12, -15, and -18, macrophage inflammatory protein 1 (MIP-1), monocyte chemotactic protein 1 (MCP-1), and granulocyte macrophage colony-stimulating factor (GM-CSF).[10] A cardinal feature of sarcoidosis is the presence of CD4+ T cells that interact with APCs to initiate the formation and maintenance of granulomas. CD4+ T cells release interleukin-2 and interferon-γ. Activated CD4+ cells differentiate into type 1 helper (Th1)-like cells and secrete predominantly interleukin-2 and interferon-γ. The efficiency of antigen processing, antigen presentation, and cytokine release is probably under genetic control; evidence strongly supports a role for macrophage HLA and BTNL2 alleles in sarcoidosis susceptibility and phenotype.[11,12] However, T-cell genes that may confer a predisposition to sarcoidosis or affect the phenotype have not yet been identified. Sarcoidal granulomas are organized, structured masses composed of macrophages and their derivatives, epithelioid cells, giant cells, and T cells. Sarcoidal granulomas may persist, resolve, or lead to fibrosis. Alveolar macrophages activated in the context of a predominant type 2 helper (Th2) T-cell response appear to stimulate fibroblast proliferation and collagen production, leading to progressive fibrosis. Adapted with permission from Iannuzzi and colleagues.[4]

studies, etiologic agents for sarcoidosis remain elusive, although associations with certain infectious agents as well as occupational and environmental exposures including certain drugs have been noted. Numerous microorganisms including mycobacteria, cutibacteria, and some lymphotropic viruses have been implicated as possible etiologic agents of sarcoidosis based on presence of these organisms in the tissue of patients of sarcoid patients. Similarly, occupational and environmental exposure to inorganic dust is thought to be play a role based on sarcoid like granulomas in individuals exposed to silica, beryllium zirconium, and aluminum.[8] Nevertheless, the pathogenesis of granulomas appears to be a highly complex process involving immune cells and their mediators in a genetically susceptible host (Figure 1).[4] In the lungs, dendritic cells travel to lymph nodes for the initial presentation of antigen, leading to activation of latent circulating CD4+ lymphocytes although macrophages can also act as the antigen presenting cells. The central chemokine in active sarcoidosis is interferon (INF)-gamma but IL-2, IL-12, and TNF-alpha are also important, and pulmonary-derived exosomes may play an important role in promoting inflammation. The oligoclonal expansion of CD4+ T cells suggests that a pathogenic antigen initiates the disease. The amplification of CD4+ cells appears to correlate with the degree of alveolitis in the lungs, while the granuloma formation typically is along the lymphatic tracks, which course along the bronchovascular bundle and through interlobular septa.[9]

Diagnosis of pulmonary sarcoidosis

The diagnosis of sarcoidosis requires a stepwise approach including clinical, radiologic, and histopathologic findings[13] (Figures 2 and 3). About 90% of patients with sarcoidosis have pulmonary involvement.[1] In about one-half of patients, the disease is detected incidentally by radiographic abnormalities on a routine chest radiograph, the most common of which are bilateral hilar adenopathy and parenchymal reticulonodular opacities.[14] Bronchoscopy with bronchoalveolar lavage, transbronchial biopsies, and fine-needle aspiration of hilar and mediastinal lymph nodes is often undertaken to rule out infection and establish the presence of granulomas. Table 1 summarizes the different clinical presentations of pulmonary sarcoidosis with their associated imaging and pulmonary function test findings.

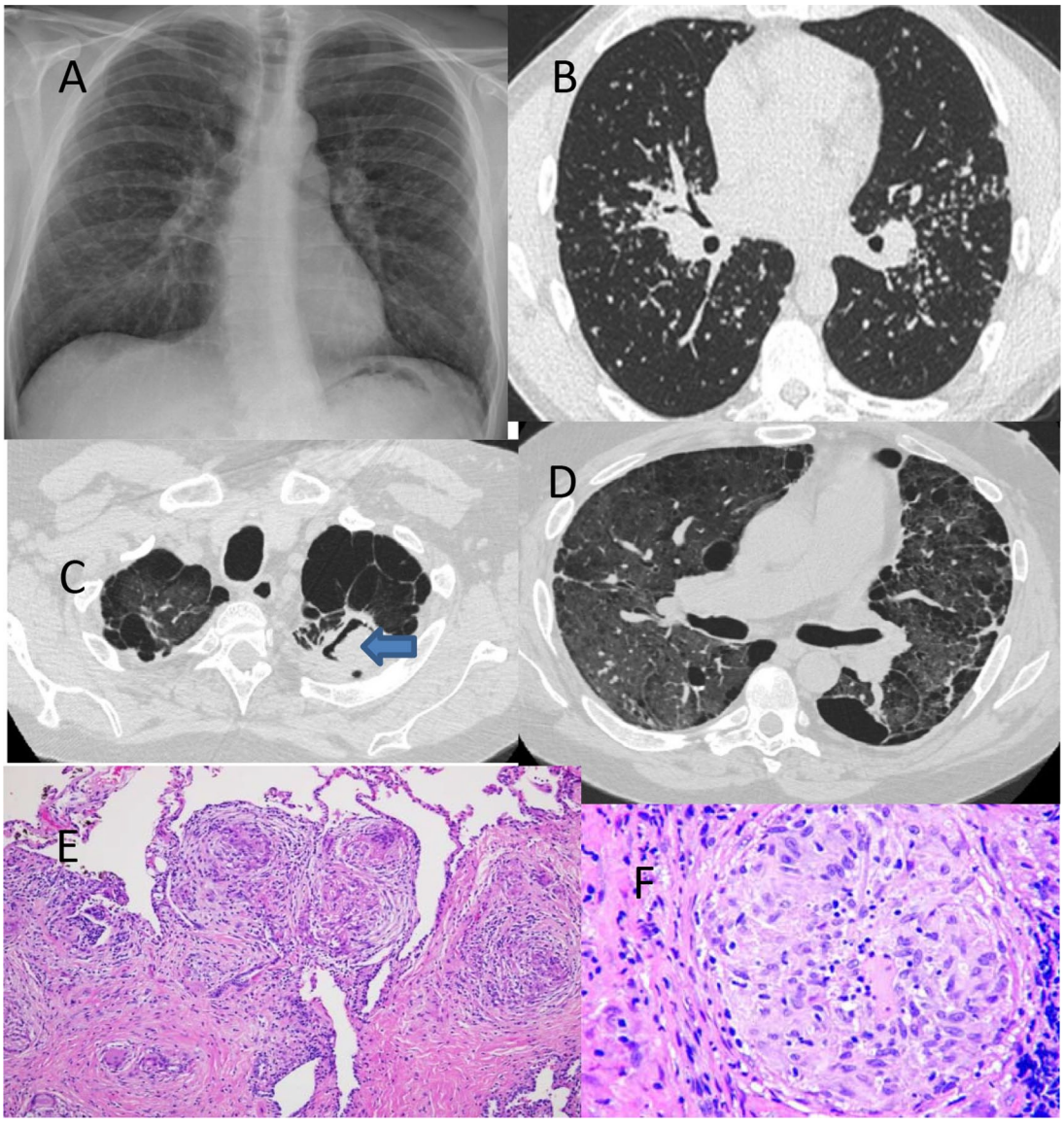

Figure 2. Radiology and pathology of pulmonary sarcoidosis: A- Plain chest radiograph showing bilateral hilar adenopathy and interstitial infiltrates, B- axial CT scan of the chest showing inflammatory sarcoidosis with micronodules in a typical perilymphatic distribution, C- axial CT scan of the chest from a patient showing chronic pulmonary sarcoidosis and a mycetoma (arrow), D- axial CT scan of the chest from the same patient showing fibrocystic changes, E- open lung biopsy specimen showing granulomas along the alveolar septa and bronchovascular bundle, F-a high power magnification view of a sarcoid granuloma.

Clinical symptoms and signs

Sarcoidosis typically presents in patients between the third and the sixth decade, with disease onset about a decade earlier in Blacks than in Whites.[15] Often called a great mimicker, clinical symptoms and signs of the disease can be variable. Common presenting pulmonary symptoms include cough and dyspnea; wheezing and airway reactivity are the common manifestations of the endobronchial phenotype but can occur in patients with fibrosis centered on the airways.[16] If bronchiectasis is present, patients may present with chronic purulent sputum production and hemoptysis. Additionally, some patients can present with pulmonary infections, including mycetomas in cavitary lesions. While respiratory failure is possible, precipitous declines from acute exacerbations are not common, in contrast to patients with idiopathic pulmonary fibrosis.[16] This is likely because the process of granuloma formation is rather slow. However, these patients can have acute decompensations due to other complications, including

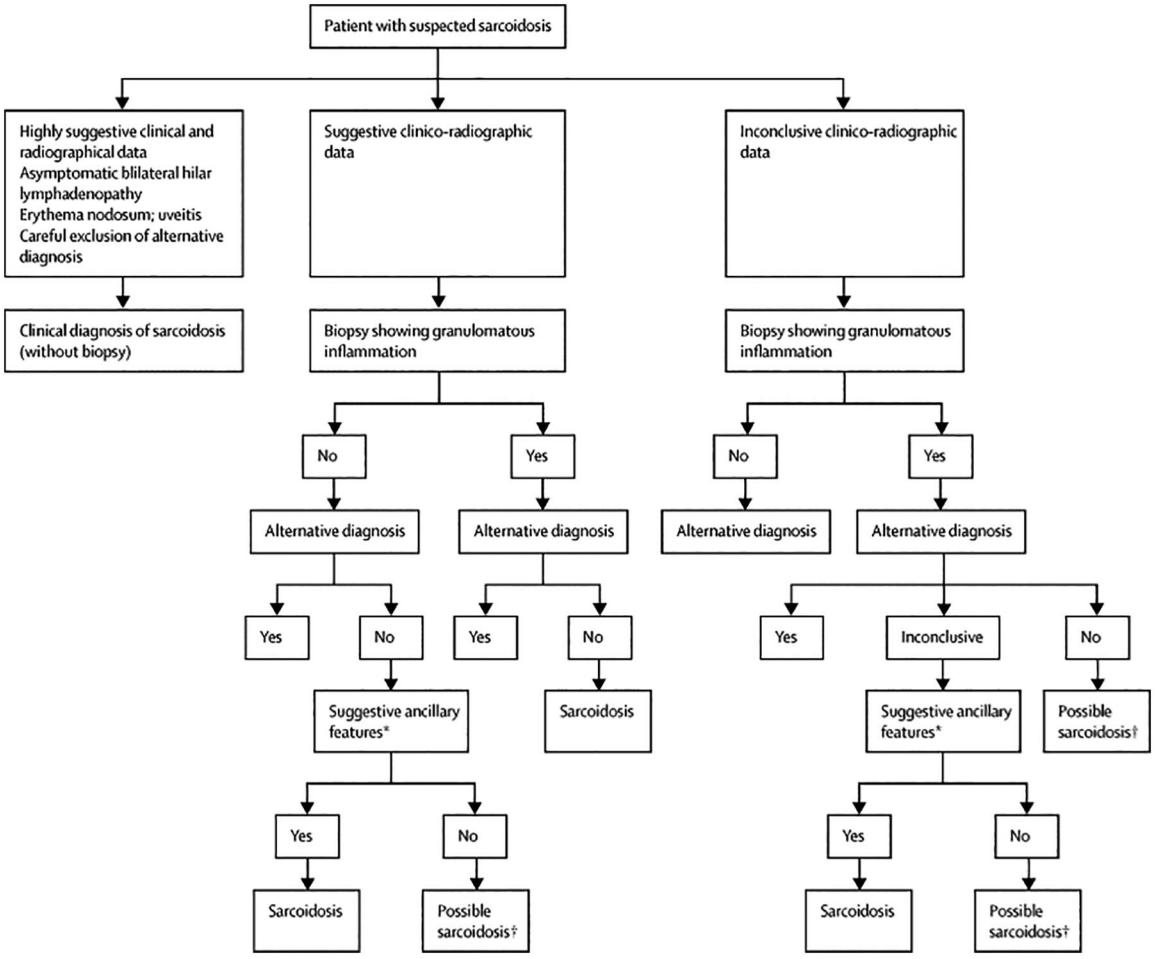

Figure 3. Proposed diagnostic algorithm for pulmonary sarcoidosis (reproduced with permission from Spagnolo and colleagues[14]).

acute infections, heart failure, and pulmonary embolism,[17] which are all more common in patients with sarcoidosis than the general population. The development of sarcoid associated pulmonary hypertension (SAPH) should be suspected in patients with disproportionate decreases in their diffusion capacity compared with spirometry and lung volumes.[6] There have been increasing reports of combined sarcoidosis and idiopathic pulmonary fibrosis (CSIPF); this entity should be considered in the appropriate setting.[18]

On physical examination, patients can have variable degrees of tachypnea, tachycardia, and hypoxemia. Crackles are uncommon even with significant parenchymal fibrosis, but endobronchial lesions or bronchocentric fibrosis can lead to wheezing.[17] Digital clubbing is rare and is typically associated with advanced pulmonary fibrosis.

Imaging

Historically, the findings on plain chest radiography have been used to evaluate and categorize thoracic sarcoidosis into different stages, as first described by Siltbach half a century ago.[19] These stages are useful as an anatomic guide to lung involvement as well as prognostication; specifically, spontaneous remission has been noted to occur in 60–90% of patient with stage I disease characterized by mediastinal and hilar adenopathy alone, 40–70% with stage 2 disease defined by the presence of both mediastinal adenopathy and pulmonary infiltration, 10–20% with stage 3 disease with pulmonary infiltration alone, and 0% in stage 4 disease characterized by fibrosis. With the advent of computerized tomography, especially high resolution computed tomography (HRCT), the diagnostic accuracy of sarcoidosis has been much higher.[20] Moreover, HRCT findings may correlate much better with functional

Table 1. Clinical presentations of pulmonary sarcoidosis with associated imaging and pulmonary function test findings.

Clinical phenotype	Clinical features	Imaging Findings	Pulmonary functions
Inflammatory parenchymal pulmonary sarcoidosis	Exertional dyspnea, cough	Bilateral hilar adenopathy, upper lobe predominant reticulonodular opacities along intralobular septa and bronchovascular bundles, ground glass opacities	Normal or a mild to moderate restrictive ventilatory defect or a mixed pattern
Fibrotic pulmonary parenchymal sarcoidosis	Exertional dyspnea, dry cough, chest tightness	Reticular infiltrates, dense linear bands, traction bronchiectasis, airway distortion	Restrictive ventilatory defect with decreased diffusion capacity
Endobronchial sarcoidosis	Dry cough	Airway distortion	Obstructive airway disease, Bronchial hyperreactivity
Pleural disease	Chest pain, pleural rub	Pleural effusion, pneumothorax	Restrictive ventilator defect
Pulmonary vascular Disease	Exertional dyspnea, palpitations, edema, presyncope or syncope	Enlarged pulmonary artery, right ventricular dilation	Decreased diffusion capacity, often with restrictive ventilator defect due to associated interstitial lung disease
Pulmonary sarcoid with infectious complications	Sputum production related to bronchiectasis, hemoptysis possible with mycetomas	Bronchiectasis, Mycetoma	Mixed pattern
Lofgren's syndrome	Acute onset, erythema nodosum, fever, arthritis, bilateral hilar adenopathy	Bilateral hilar adenopathy	Often normal

respiratory impairment.[21] There are several findings typical of sarcoidosis on HRCT including mediastinal lymphadenopathy, bilateral perihilar opacities, micro and macronodules, perilymphatic distribution, fibrotic changes, with a propensity for upper- and mid-lung predominance for parenchymal abnormalities.[20] In fact, in the appropriate clinical setting, a combination of micronodules with a perilymphatic and upper lobe distribution, together with subcarinal and symmetrical hilar lymph node enlargement is practically diagnostic of sarcoidosis and lung biopsy may not be required[14] (Table 1). Atypical HRCT findings include unilateral or isolated lymphadenopathy, airspace consolidation, ground-glass opacities, fibrocystic changes, linear opacities, milliary opacities, evidence of airway involvement (mosaic attenuation), tracheobronchial abnormalities (diffuse wall thickening and luminal narrowing), pleural disease, and mycetomas. The main pulmonary trunk may be enlarged and there might be evidence of right ventricular strain if pulmonary hypertension (PH) is present.[22]

Pulmonary function testing

Pulmonary function testing (PFT) in patients with sarcoidosis can be variable depending on the extent and severity of disease as well as the presence of complications. A majority of patients have normal PFTs.[23] The most common abnormality is a restrictive ventilatory defect with a reduction in the single breath diffusion capacity for carbon monoxide (DLCO), which can be due to parenchymal involvement or due to the presence of PH.[24] However, any PFT pattern may be seen including restrictive ventilatory defects, obstructive disease, mixed obstruction/restriction, or an isolated reduction in the DLCO. Although airflow obstruction can be seen with all radiological stages, it appears to increase in prevalence with increasing chest radiographic stage.[25] However, airflow obstruction usually does not respond to bronchodilators so routine use of these agents is not recommended. It is noteworthy that baseline PFTs do not predict the likelihood of disease progression; rather, the composite physiologic index

derived from predicted values of FVC, FEV1, and DLCO, may be a better predictor of mortality.[26] As such, although no follow-up guidelines exist, most experts recommend at least annual PFTs to monitor disease progression.

Histopathology

Because the pathologic hallmark of pulmonary sarcoidosis is granulomatous inflammation, a histological specimen is usually obtained to support the clinic-radiological diagnosis. This was traditionally obtained through transbronchial biopsies, frequently coupled with endobronchial biopsies or conventional transbronchial needle aspiration of lymph nodes to increase the yield.[27] Over the last decade, the technique of endosonography has been increasingly used for the diagnosis of pulmonary sarcoidosis; it involves real-time ultrasound guidance to image the hilar and mediastinal lymph nodes *via* the bronchus (endobronchial ultrasound, EBUS) or the esophagus (transesophageal endoscopic ultrasound, EUS) to help sample the lymph nodes by fine-needle aspiration. Both EBUS and EUS have an overall diagnostic accuracy exceeding 80%, as demonstrated by a large randomized clinical trial.[28] This is further enhanced by the availability of rapid onsite evaluation (ROSE) by cytopathologists, which can increase the sensitivity and specificity to 87.8% and 91%, respectively.[29] The combination of EBUS guided transbronchial needle biopsy (TBNA) of the lymph nodes and transbronchial biopsies of the parenchyma leads to significantly greater diagnostic accuracy; as such, for patients with both nodal and parenchymal disease, both may be used in conjunction. For patients with stage I disease alone, EBUS would be the modality of choice, while for patients without mediastinal adenopathy, transbronchial biopsies alone may still be required. Bronchoalveolar lavage during the bronchoscopy will aid in evaluating for granulomatous infections that may mimic the diagnosis. Bronchoalveolar lavage with a cell count may further assist in selected cases with predominant lymphocytosis, since the presence of CD4 lymphocytes >CD8 lymphocytes (i.e. a CD4/CD8 ratio >1) are consistent with a diagnosis of sarcoidosis.[14]

Principles of management

The general principles of management of pulmonary sarcoidosis are to alleviate symptoms, prevent progression of disease and the development of irreversible end-organ damage by suppressing and limiting the burden of granulomatous inflammation, and thereby prevent mortality. However, most studies looking at therapies for pulmonary sarcoidosis are small, and there have been very few large clinical trials. As such, most of the recommendations for the management for this condition are based on weak evidence or expert opinion only. However, supportive therapy in the form of smoking cessation measures, immunization against pneumococcus and influenza, and pulmonary rehabilitation should be provided to all patients. Patients with pulmonary fibrosis should be assessed for any supplemental oxygen needs and managed according to standards of care.

A large number of patients are asymptomatic, and many patients will have no progression or even resolution of disease without any specific therapy. The typical example is a patient with Lofgren's syndrome characterized by acute onset of symptoms, bilateral hilar lymphadenopathy, erythema nodosum, fever, and arthritis; this is generally associated with little pulmonary symptoms and a favorable prognosis.[30] However, for patients with worsening respiratory symptoms, severe pulmonary function impairment, or substantial functional deterioration and major radiological progression, most experts would agree on initiating treatment, usually with corticosteroids at the inception. Once treatment is initiated, it is usually continued for about a year. As a result, clear communication to patients about the details of treatment including adverse effects of medications is vital. In 2014, Walsh and colleagues described an algorithm for predicting survival for patients with pulmonary sarcoidosis integrating the composite physiological index and two HRCT variables for fibrosis and pulmonary artery diameter, but it was based on a single-center, retrospective study.[31] A recent study looking at prognostic strength of factors in predicting respiratory death in a large cohort of patients with sarcoidosis with at least 8 years of follow up showed that older age, extensive fibrosis on HRCT scanning, and the presence of PH were the most important risk factors.[32] Consequently, in patients presenting with severe fibrotic disease or pulmonary arterial hypertension not responsive to therapy, lung transplantation or palliative care should be explored early.

Assessment of response to therapy in sarcoidosis requires a combination of clinical symptoms, physical examination, PFT and radiographic

imaging. Generally, a change in FVC of 10% or DLCO of 20% is considered significant in PFT.[33] Although an insensitive test for the diagnosis of sarcoidosis, angiotensin converting enzyme (ACE) levels can be used as an adjunct to monitor disease activity and response to treatment, but can be low in the presence ACE inhibitors[34] Other biomarkers that could be useful include soluble interlukin-2 receptor (sIL-2R), neotropin, chitotriosidate (CTO), lymphocyte counts, and certain chemokines, but their usefulness needs to be validated in larger studies.[35] More recently, an outcome measures set was defined for pulmonary sarcoidosis based on a multicenter initiative consisting of seven outcome measures: mortality, pulmonary function, soluble interleukin-2 receptor change as an activity biomarker, weight gain, quality of life, osteoporosis, and clinical outcome status.[36] It is hoped that this will establish a common ground for future studies on both monitoring and treatment of this condition. Similarly, imaging modalities including CT scan with CT activity score and positron emission tomography (PET)/CT are gaining increased attraction as potential tools to measure efficacy of treatment although further studies are needed before recommending either of them.[11,12]

Treatment options

Sarcoidosis is an orphan disease and its treatment lacks standardization, largely due to the paucity of good quality clinical trials. In fact, the last official consensus statement by different international societies including the American Thoracic Society (ATS), European Respiratory Society (ERS), and World Association of Sarcoid and Other Granulomatous diseases (WASOG) was almost two decades ago.[37] A Delphi consensus study was undertaken about a decade ago at the annual CHEST meeting in October 2008, where several experts reached a consensus concerning several aspects of the treatment of pulmonary sarcoidosis.[38] However, many issues remained unresolved, which underscored potential areas for future research. Figure 2 shows a suggested algorithm for the management of pulmonary sarcoidosis. We will discuss the currently available pharmacologic agents for pulmonary sarcoidosis in the following section. Table 2 summarizes the pharmacologic agents commonly used in the treatment of pulmonary sarcoidosis. Figure 4 presents a possible algorithm in the management of pulmonary sarcoidosis with levels of evidence for different pharmacologic agents.[3] Because the clinical course of pulmonary sarcoidosis is variable and the adverse events with the available therapies are not insignificant, it is very essential to engage patients throughout the course of diagnosis and treatment. Patients should understand that most of the treatment is aimed at symptom relief and improvement of quality of life and treatment may not necessarily improve survival.

Glucocorticoids

Glucocorticoids have been the first line of treatment for pulmonary sarcoidosis for decades since they are known to suppress and limit the burden of granulomatous inflammation with good efficacy. They act by transcriptional regulation of glucocorticoid-receptor target genes as well as *via* nongenomic signal transduction pathways in lymphocytes and alveolar macrophages.[4] Indeed, most of the available data suggests that oral glucocorticoids improve respiratory symptoms, spirometry, and radiographic abnormalities.[39] However, oral steroids are also associated with several side effects and the patient should be fully counseled on these so they can make an informed decision. Also, despite several years of clinical use of corticosteroids in pulmonary sarcoidosis and several randomized controlled trials, there is still wide variability in suggested dosage, duration, and tapering regimens although it is generally agreed that the duration of treatment should be in the order of several months. The ATS/ERS/WASOG statement in 1999 recommended 20–40 mg daily of prednisone for 1–3 months followed by a maintenance dose for 6–9 months.[37] The Delphi consensus study in 2008 concluded that 40 mg of daily prednisone equivalent was the maximum dose recommended for the treatment of acute pulmonary sarcoidosis and tapering to 10 mg of daily prednisone equivalent for chronic pulmonary sarcoidosis was considered a successful taper.[38] Regardless, because of the side effects associated with chronic steroid use, it is prudent to taper steroids to the lowest effective and best tolerated dose. Steroid sparing cytotoxic agents should be considered if it is not possible to taper prednisone below 10 mg daily. The rate of relapse of disease after stopping steroids has been observed to range from 14% to 74% with half of these occurring between 2 and 6 months thereafter; hence, generally patients are treated for about a year. In as many as 20% of the patients, relapses can occur after 12 months of therapy but reintroduction of steroids

Table 2. Pharmacologic agents commonly used in the treatment of pulmonary sarcoidosis.

Drug	Mechanism of action	Dose	Side effects	Monitoring
Corticosteroids	Transcriptional regulation of glucocorticoid-receptor target genes, modulation of nongenomic signal transduction in lymphocytes	20–40 mg/day for 6–8 weeks then to be gradually tapered to maintenance of 5–10 mg/day	Thrush, hyperglycemia, fluid gain, hypertension, myopathy, osteoporosis, cataracts, glaucoma	Blood sugars, blood pressure
Methotrexate	Folate antimetabolite that inhigbits DNA synthesis, repair and cellular replication	5–20 mg/week	Nausea/emesis, stomatitis, hepatitis, bone marrow suppression, pneumonitis	CBC, LFTs
Azathioprine	Inhibition of purine synthesis	50–200 mg/day	Nausea, myalgia, hepatitis, bone marrow suppression	CBC, LFTs
Lefluonamide	Inhibition of pyrimidine synthesis	10–20 mg/day	Diarrhea, nausea, hepatitis, alopecia, neuropathy	CBC, LFTs
Mycophenolate	Inhibitor of inosine monophosphate dehydrogenase leading to inhibition of nucleotide synthesis	500–3000 mg/day	Nausea, diarrhea, hepatitis, bone marrow suppression	CBC, LFTs
Infliximab	Monoclonal antibody against tumor necrosis factor-α	3–5 mg/kg IV, then 2 weeks later, then every 4–8 weeks	Infusion reactions, Infections including TB, malignancies including lymphoma	Testing for latent TB and viral hepatitis before starting. Symptoms of infection including tuberculosis
Adalimumab	Monoclonal antibody against tumor necrosis factor-α	40–80 mg every 1–2 weeks	Infusion reactions, Infections including tuberculosis, malignancies	Testing for latent TB and viral hepatitis before starting. Symptoms of infection including tuberculosis

CBC, Complete blood count; LFT, liver function tests; TB, tuberculosis.

usually leads to stabilization of disease.[40] A recent study identified smoking history and increased percentage of circulating neutrophils (>70%) as two significant predictors of relapse in pulmonary sarcoidosis treated with steroids.[10]

Inhaled glucocorticoids are generally not recommended for the initial treatment of pulmonary sarcoidosis due to of lack of efficacy and inadequate data.[41] However, they may be useful adjuncts if cough and airway hyperreactivity are predominant symptoms, or if the pulmonary symptoms and lung function abnormalities are mild. They could also be considered as maintenance agents if only low dose oral prednisone is needed. Adrenocorticotropic hormone, which works by stimulation of cortisol production by adrenal glands, has been looked at as an alternative to systemic steroids but does not have any improved efficacy or safety than oral steroids; it is available as injection only and cost may be prohibitive to many patients. Consequently, it cannot be recommended routinely for the treatment of pulmonary sarcoidosis although a repository corticotropin could be considered for some patients with refractory pulmonary sarcoidosis.[42] There are no published data on the use of intravenous steroids on pulmonary sarcoidosis although they are sometimes utilized in the inpatient setting. Similarly, there is no data on other oral steroids besides oral prednisone.

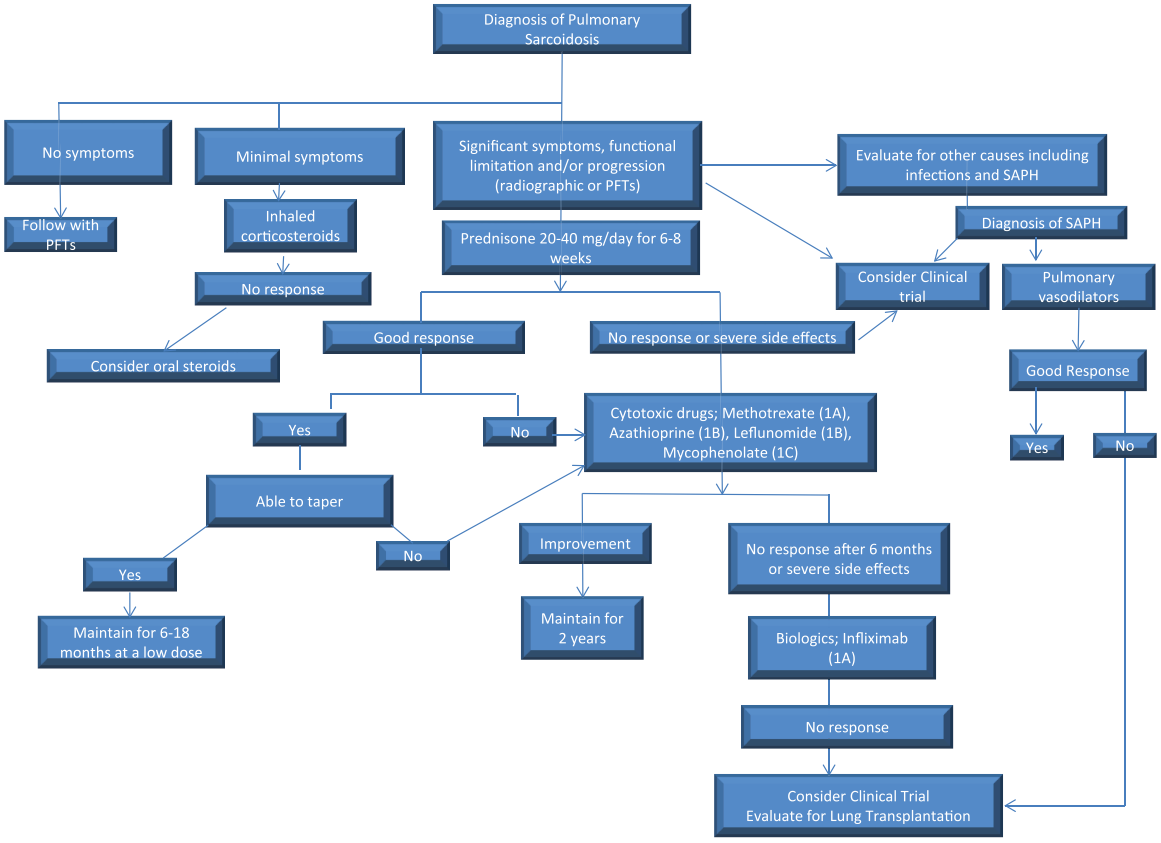

Figure 4. Treatment strategy for pulmonary sarcoidosis with levels of evidence for different agents. This is developed from best available data and expert opinion. Adapted with permission from Zhou and colleagues.[3]

Cytotoxic agents

Some patients with chronic pulmonary sarcoidosis cannot be tapered below 10 mg daily of prednisone without relapses while others cannot tolerate long-term side effects of steroids even at a modest dose. Still others continue to have progressive and disabling respiratory impairment despite modest doses of steroids. These subsets of patients, generally constituting about 10% of patients with sarcoidosis are treated with one of many cytotoxic medications used as steroid-sparing alternatives, the most common being methotrexate (MTX).[5] All cytotoxic agents have the potential of teratogenicity; therefore, women of reproductive potential should be counseled accordingly, and if they desire a pregnancy, they should be referred to a center with expertise in managing such cases. All the cytotoxic agents currently used also cause varying degrees of cytopenias and have a potential for hepatotoxicity as well as opportunistic infections; thus regular monitoring of complete blood count (CBC) and liver function tests (LFT) as well as having a low index of suspicion for opportunistic infections is important.

Methotrexate

Oral MTX is the most commonly used cytotoxic agent for pulmonary sarcoidosis and is also used in a variety of other automimmune conditions. In fact, the Delphi consensus study in 2008 recommended this as the preferred second-line agent.[38] It acts by inhibiting the folic acid reductase enzyme, and has both immunosuppressive and anti-inflammatory properties. A small randomized controlled trial established its steroid-sparing effect in pulmonary sarcoidosis about two decades ago,[43] which was followed by several supportive small series and case reports. More recently, WASOG laid out the recommendations for MTX in sarcoidosis based on a review of the literature over the years, coupled with expert opinion.[44] Overall, about 60% of patients with sarcoidosis seem to respond to MTX.[45] Generally, the starting dose of MTX for sarcoidosis is 5 mg

weekly; it is increased gradually by increments of 2.5 mg every 2 weeks until a dose of 10–15 mg per week is reached.[44] If patients develop refractory nausea/vomiting with oral MTX, it can be switched to the intramuscular route. Because the effects of MTX may not be seen until 6 months after initiation, tapering of steroids should be delayed for several months after initiating MTX.

Common adverse effects of MTX include leukopenia, nausea/vomiting and mucositis. Drug-induced pneumonitis is a rare but serious dose-dependent complication occurring months to years after treatment and has to be considered with worsening lung disease.[46] Prior to the initiation of therapy, it is important to obtain baseline LFT, CBC, serum creatinine, and serologies for hepatitis B and C viruses as well as testing for latent mycobacterium tuberculosis infection.[47] Patients with underlying liver disease, advanced chronic kidney disease (GFR <30 ml/min), and chronic viral hepatitis are not candidates for MTX therapy.

Other antimetabolites

Azathioprine (AZT) is probably the second most commonly used antimetabolite after MTX. Although not as widely studied as MTX, its lack of potential pulmonary toxicity may be more attractive to some patients. A retrospective review did suggest a similar efficacy between AZT and MTX on lung function, although infection rates were higher with AZT.[48] The starting dose of AZT is usually 50 mg daily, with titration every 2 weeks by 25 mg to a maximum dose of 200 mg daily. Patients with genetic polymorphisms of the enzyme thiopurine-S-methyltransferase (TPMT) resulting in low levels of enzymes are at increased risk of toxicity and might need lower doses; therefore, testing for TPMT enzyme activity is prudent.

Lefluonamide is another antimetabolite that can be used as an adjunct to MTX or, on occasion, by itself in cases not adequately responsive to MTX. Although not as well studied as MTX, it seems to have a cure rate similar to MTX based on two retrospective cohort studies.[21] The typical initial dose is 10 mg daily, which can be increased in a few weeks to 20 mg daily if well tolerated.

Mycophenolate mofetil is used in many interstitial lung diseases associated with connective tissue diseases but its role in pulmonary sarcoidosis is not as well established. Two small studies have shown significant steroid-sparing capability without consistent findings on other end-points.[49,50] The usual starting dose is 500 mg twice daily, which can be increased every few weeks by 250 mg to a maximum dose of 1500 mg twice daily.

Biological agents

In patients with sarcoidosis who do not respond to cytotoxic drugs, biologic agents targeting tumor necrosis factor (TNF) are used as third line agents based on the observation that TNF-α appears to maintain granuloma formation, although data supporting the use of these agents is limited. The most commonly used of those agents is infliximab, which is a chimeric, humanized monoclonal antibody that neutralizes TNF-α. A randomized trial of infliximab in 138 patients by Baughman and colleagues in 2006 demonstrated a statistically significant improvement in percent predicted FVC at 24 weeks in the infliximab group although the magnitude of improvement was small.[51] It is possible that a subset of patients with peripheral blood CD4+ T cell lymphopenia and resistance to first and second line agents might respond to infliximab.[52] Adalimumab, a fully human anti-TNF-α antibody was found to be efficacious in a cohort of patients with pulmonary sarcoidosis who developed intolerance to infliximab,[53] and thus seems promising. On the other hand, a small preliminary trial of etanercept, a soluble fusion protein that binds TNF-α, done several years ago, was stopped early after noting treatment failure in 11 out of 17 enrolled patients.[54] A trial of two monoclonal antibodies ustekinumab and golimumab inhibiting IL-12/IL-23, respectively, as well as TNF-α did not show a difference in change in FVC predicted compared with placebo in a trial.[55] Potential side effects of TNF antagonists include reactivation of latent infections including tuberculosis and viral hepatitis and therefore adequate pretreatment testing including testing for latent tuberculosis as well as monitoring during treatment is essential. The combination of these agents with MTX or AZT appears to inhibit antibody formation to those agents and improve disease control in rheumatoid arthritis and Crohn's disease, but there is no data in sarcoidosis to support this recommendation.

Other agents

Cyclophosphamide is rarely used in sarcoidosis and is reserved for refractory or progressive disease.[56] It

is an alkylating agent whose metabolites deplete lymphocytes and it also has anti-inflammatory properties. Toxicities include cytopenias, risk of infections, hemorrhagic cystitis, carcinoma of the bladder, and gastrointestinal side effects including hepatotoxicity.

There is interest in antimycobacterial therapy as a potential therapeutic option in sarcoidosis since there is evidence that nontuberculous mycobacteria might be implicated in the pathogenesis of the disease. An open label trial of concomitant levofloxacin, ethambutol, azithromycin, and rifampin (CLEAR) suggested that this therapy improved quality of life, 6-min walk (6MW) distance, and vital capacity.[57] There is currently an ongoing phase II trial investigating this therapeutic regimen further.

Other agents of interest include Canakinumab (a recombinant human monoclonal interleukin-1B antibody), rituximab (monoclonal antibody against CD-20), tofacitinib (jankus kinase-signal transducer and activator of transcription inhibitor), hydroxycholoroquine, and chloroquine (antimalarial drugs with immunomodulating properties).

Treatment of pulmonary hypertension in sarcoidosis

PH is common in patients with sarcoidosis, with prevalence estimates varying from 5% to 73% of all patients based on population studied; for example, this number is much higher in patients on the lung transplant waiting list.[58,59] There are many potential contributors to the development of SAPH, including most commonly fibrosis-associated obliteration of the vascular bed, hypoxia-induced pulmonary vasoconstriction, left ventricular dysfunction, pulmonary venoocclusive disease-like lesions, and, more rarely, pulmonary vascular compression by mediastinal lymphadenopathy, granulomatous arteritis, and portopulmonary hypertension secondary to sarcoid liver disease.[60]

As with all patients with PH, patients with SAPH should be provided with supportive measures such as oxygen supplementation, smoking cessation strategies, vaccinations, and treatment of sleep-disordered breathing. The optimal pharmacotherapy of SAPH remains challenging since there is a lack of randomized trials in these patients, and the presence of parenchymal lung disease makes treatment difficult in general. The role of corticosteroids as a primary treatment of SAPH is controversial, and is probably of benefit in a very limited number of patients with active inflammation or compression of the proximal pulmonary arteries by adenopathy. The majority of SAPH patients have significant parenchymal lung disease; most commonly stage 4, and are very unlikely to improve with steroids. Available data suggests that pulmonary vasodilator therapy may improve the hemodynamic profile of patients with SAPH, but whether this translates to sustained improvements in functional capacity and patient outcomes is yet to be determined. The most studied class of pulmonary vasodilators in SAPH is the endothelin receptor antagonists, which have been demonstrated to improve pulmonary hemodynamics, but without improvement in the 6MW distance.[61,62] Several case series have reported on the efficacy of PDE-5 inhibitors in SAPH, with most of them showing improved functional status and echocardiographic parameters.[63–65] An open label prospective study of inhaled iloprost in 22 SAPH patients provided data suggestive of an improvement in quality of life and hemodynamics.[66] At this time, firm recommendations are lacking about the role of pulmonary vasodilator therapy for the treatment of SAPH. If such therapy is undertaken, it should be in the context of a clinical trial or at an expert center with experience in the management of this complex disorder.

It is also very important to evaluate patients with pulmonary sarcoidosis for cardiac sarcoidosis, especially if they have developed PH. Cardiac sarcoidosis causes left ventricular dysfunction and contributes to PH. Moreover, cardiac sarcoidosis can be life-threatening due to conduction abnormalities; therefore, aggressive treatment should be pursued.

Lung transplantation

Lung transplantation may be an option in a minority of patients with sarcoidosis when all medical therapy has been exhausted. Sarcoidosis accounts for about 2.5% of all lung transplants but the International Society for Heart and Lung Transplantation (ISHLT) does not have specific guidelines for the referral of patients with sarcoidosis for lung transplantation due to paucity of data.[67] Generally, however, patients with NYHA functional class 3 and 4 symptoms, resting hypoxemia

or severe PH warrant referral. Evaluation of other organ involvement, especially cardiac involvement, is vital to assess for lung transplant candidacy; patients with concurrent cardiac sarcoidosis in particular, have a poorer prognosis and may need combined heart and lung transplantation.[68] Patients with mycetomas and suppurative bronchiectasis mandate bilateral lung transplantation as well as aggressive antimicrobial therapy in the perioperative period. Lung transplantation in patients with sarcoidosis may be challenging for the transplant surgeons due to variable presence of extensive pleural thickening and adhesions, mycetomas, bulky hilar adenopathy, perihilar fibrosis, and concomitant PH. Long-term outcomes after lung transplantation for sarcoidosis in general are comparable to those for other indications,[69] although short-term outcomes may be slightly worse.[70] In general, patients with pulmonary sarcoidosis without cardiac involvement do well without simultaneous heart transplantation even in the presence of severe PH and right ventricular dysfunction because right ventricle remodels afterwards, but the presence of significant cardiac sarcoidosis often requires a combined heart and lung transplantation. Sarcoid granulomas tend to recur in the allograft in about two-thirds of cases, but this is usually a histopathologic curiosity with most patients remaining asymptomatic.[6]

Conclusion

Pulmonary sarcoidosis is an orphan disease characterized by a highly variable presentation, which can make the diagnosis challenging. Moreover, it is associated with unpredictable progression and incomplete response to therapy, leading to significant morbidity in affected patients. Diagnosis and assessment usually requires a comprehensive approach taking into account the clinical presentation, imaging, PFT, and, invariably, histopathologic confirmation. It is important to take an individualized approach by engaging patients in all decisions regarding diagnostic parameters and therapeutic options. Optimizing the treatment of pulmonary sarcoidosis generally involves supportive treatment, consideration of systemic steroids, with or without second-line agents, as well as management of comorbidities including PH, infections and extrapulmonary manifestations.

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Conflict of interest statement

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