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ONLINE EXCLUSIVE

Sarcoidosis: An FP's primer on an enigmatic disease

Management includes ruling out alternate diagnoses, identifying occult/overt organ involvement, determining treatment, and recognizing worrisome features.

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PRACTICE RECOMMENDATIONS

› *Consider biopsy to aid in diagnosing sarcoidosis; it may be avoided with a high clinical suspicion for sarcoidosis (eg, Löfgren syndrome, lupus pernio, or Heerfordt syndrome).* (C)

› *Rule out alternative diagnoses such as infection, malignancy, collagen vascular disease, and vasculitis.* (C)

› *Identify extra-pulmonary organ involvement, as clinically indicated, by screening with a baseline eye examination; complete blood count; creatinine, alkaline phosphatase, and calcium levels; electrocardiogram, and other organ-specific studies.* (C)

› *Make a patient-centered decision whether to begin anti-inflammatory treatment based on symptomatology and risk of organ failure or death.* (C)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence

(B) Inconsistent or limited-quality patient-oriented evidence

(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

Sarcoidosis is a multisystem inflammatory disease of unclear etiology that primarily affects the lungs. It can occur at any age but usually develops before the age of 50 years, with an initial peak incidence at 20 to 29 years and a second peak incidence after 50 years of age, especially among women in Scandinavia and Japan.[1] Sarcoidosis affects men and women of all racial and ethnic groups throughout the world, but differences based on race, sex, and geography are noted.[1]

The highest rates are reported in northern European and African-American individuals, particularly in women.[1,2] The adjusted annual incidence of sarcoidosis among African Americans is approximately 3 times that among White Americans[3] and is more likely to be chronic and fatal in African Americans.[3] The disease can be familial with a possible recessive inheritance mode with incomplete penetrance.[4] Risk of sarcoidosis in monozygotic twins appears to be 80 times greater than that in the general population, which supports genetic factors accounting for two-thirds of disease susceptibility.[5]

Likely factors in the development of sarcoidosis

The exact cause of sarcoidosis is unknown, but we have insights into its pathogenesis and potential triggers.[1,6-9] Genes involved are being identified: class I and II human leukocyte antigen (HLA) molecules are most consistently associated with risk of sarcoidosis. Environmental exposures can activate the innate immune system and precondition a susceptible individual to react to potential causative antigens in a highly polarized, antigen-specific Th1 immune response. The epithelioid granulomatous response involves local proinflammatory cytokine production and enhanced T-cell immunity at sites of inflammation.[10] Granulomas generally form

to confine pathogens, restrict inflammation, and protect surrounding tissue.[11-13]

ACCESS (A Case Control Etiologic Study of Sarcoidosis) identified several environmental exposures such as chemicals used in the agriculture industry, mold or mildew, and musty odors at work.[14] Tobacco use was not associated with sarcoidosis.[14] Recent studies have shown positive associations with service in the US Navy,[15] metal working,[16] firefighting,[17] the handling of building supplies,[18] and onsite exposure while assisting in rescue efforts at the World Trade Center disaster.[19] Other data support the likelihood that specific environmental exposures associated with microbe-rich environments modestly increase the risk of sarcoidosis.[14] Mycobacterial and propionibacterial DNA and RNA are potentially associated with sarcoidosis.[20]

Clinical manifestations are nonspecific

The diagnosis of sarcoidosis can be difficult and delayed due to diverse organ involvement and nonspecific presentations. **TABLE 1**[21-31] shows the diverse manifestations in a patient with suspected sarcoidosis. Around 50% of the patients are asymptomatic.[23,24] Sarcoidosis is a diagnosis of exclusion, starting with a detailed history to rule out infections, occupational or environmental exposures, malignancies, and other possible disorders (**TABLE 2**).[22]

Diagnostic work-up

The primary objective of a diagnostic evaluation in most suspected cases of sarcoidosis is to corroborate the clinical and radiologic features with pathologic evidence of nonnecrotizing granulomas and to exclude other causes of granulomatous inflammation.[22]

Radiologic studies

Chest x-ray (CXR) provides diagnostic and prognostic information in the evaluation of sarcoidosis using the Scadding classification system (**FIGURE 1**).[21,25,32,33] Interobserver variability, especially between stages II and III and III and IV is the major limitation of this system.[32] At presentation, radiographs are abnormal in approximately 90% of patients.[34] Lymphadenopathy is the most common radiographic abnormality, occurring in more than two-thirds of cases, and pulmonary opacities (nodules and reticulation) with a middle to upper lobe predilection are present in 20% to 50% of patients.[1,31,35] The nodules vary in size and can coalesce and cause alveolar collapse, thus producing consolidation.[36] Linear opacities radiating laterally from the hilum into the middle and upper zones are characteristic in fibrotic disease.

High-resolution computed tomography (HRCT). Micronodules in a perilymphatic distribution with upper lobe predominance combined with subcarinal and symmetrical hilar lymph node enlargement is practically diagnostic of sarcoidosis in the right clinical context. **TABLE 3**[21,23,25,32] and **FIGURE 2**[21,23,25,32] summarize the common CT chest findings of sarcoidosis.

Advanced imaging such as (18)F-fluorodeoxyglucose positron emission tomography (PET) and magnetic resonance imaging (MRI) are used in specialized settings for advanced pulmonary, cardiac, or neurosarcoidosis.

Tissue biopsy

Skin lesions (other than erythema nodosum), eye lesions, and peripheral lymph nodes are considered the safest extrapulmonary locations for biopsy.[21,25] If pulmonary infiltrates or lymphadenopathy are present, or if extrapulmonary biopsy sites are not available, then flexible bronchoscopy with biopsy is the mainstay for tissue sampling.[25]

Bronchoalveolar lavage (BAL), transbronchial biopsy (TBB), endobronchial biopsy (EBB), and endobronchial ultrasound (EBUS) are invaluable modalities that have reduced the need for open lung biopsy. BAL in sarcoidosis can show lymphocytosis > 15% (nonspecific) and a CD4:CD8 lymphocyte ratio > 3.5 (specificity > 90%).[21,22] TBB is more sensitive than EBB; however, sensitivity overall is heightened when both of them are combined. The advent of EBUS has increased the safety and efficiency of needle aspiration of mediastinal lymph nodes. Diagnostic yield of EBUS (~80%) is superior to that with TBB and EBB (~50%), especially in stage I and II sarcoidosis.[37] The combination of EBUS with TBB improves the diagnostic yield to ~90%.[37]

CONTINUED

Sarcoidosis is a diagnosis of exclusion; one must rule out infections, occupational or environmental exposures, malignancies, and other disorders that cause granulomatous inflammation.

TABLE 1

Clinical manifestations of sarcoidosis[21-31]

Organ system	Prevalence	Clinical manifestations	Symptoms	Comments
Lungs	90%[23]	Bilateral hilar lymphadenopathy (LN) is most common; mediastinal LN, fibrotic lung disease, pulmonary hypertension[21,23,25] Rare: pleural effusion, pneumothorax,[23] necrotizing sarcoid angiitis, granulomatosis[25]	Dyspnea, dry cough, chest pain, wheezing[23,24,26]	Löfgren syndrome: triad of hilar adenopathy, erythema nodosum, arthralgias[23,25]
Skin	25%-30%[23,27]	Specific skin lesions (granulomatous) – macules/papules are most common; plaque, lupus pernio, Darier Roussy lesion[27] Nonspecific inflammatory lesions – erythema nodosum, calcinosis cutis, clubbing, and neutrophilic dermatosis[27]	Painful, pruritic rashes[27]	More common in African Americans and women[23] Specific skin lesions have predilection to tattoos and scars
Liver and spleen	Variable across studies[23]	Liver: asymptomatic elevation of liver enzymes (most common)[25] Rare: intrahepatic cholestatic syndrome, portal hypertension, hepatopulmonary syndrome, cirrhosis[31] Spleen: splenomegaly, rarely pancytopenia[23]	Fever, nausea, pruritis, abdominal pain, vomiting, anorexia, weight loss[24]	ACCESS data reported incidence of hepatic and splenic sarcoid at 11% and 7%, respectively[31]
Eyes	20%-50%[22]	Anterior uveitis (most common); chronic form leads to glaucoma Posterior uveitis Occasionally both anterior/posterior uveitis[29]	Eye pain, red eyes, blurry vision, floaters, photophobia, visual loss[25,30]	More common in women[31]
Renal Calcium disorders	7%[22] 10%-40%[21,23,25]	Renal failure due to granulomatous nephritis can occur[22,24] Asymptomatic hypercalciuria (most common), hypercalcemia, renal calculi[22,25]	Hematuria, abdominal pain	
Nervous system	5%-13%[23]	Facial nerve palsy and aseptic meningitis (most common), diabetes insipidus, cognitive dysfunction, hypopituitarism, polyneuropathy, small fiber neuropathy, spinal cord disorders, hydrocephalus, seizures[22,23,24,28]	Headache, altered mentation, cranial nerve palsies[23,24,28]	More common in women[23]
Musculo-skeletal	13%[23]	Chronic arthralgias (most common), arthritis, proximal muscle weakness, myalgias, intramuscular nodules[22,25]	Mostly asymptomatic, bone/muscle pain	
Heart	5%[23,25]	Most affected locations are left ventricular free wall and intraventricular septum (with the conducting system); hence, can manifest with bundle branch block, atrioventricular block, ventricular tachycardia, ventricular fibrillation, congestive heart failure, pericarditis, and sudden cardiac death[21,25]	Syncope, palpitations, chest pain, sudden death, heart failure[23,24]	Prevalence is around 25% in autopsy studies, indicating that the majority of cardiac involvement is silent[30]
Parotid glands	< 6%[22]	As part of Heerfordt syndrome or can manifest in isolation[22]	Swelling in parotid area	Heerfordt triad: fever, parotitis, uveitis[22,28]
Blood	4%[22]	Leukopenia	—	Rare
	22%[22]	Anemia	Fatigue, exertional dyspnea, weakness	

ACCESS, A Case Control Etiologic Study of Sarcoidosis.

TABLE 2

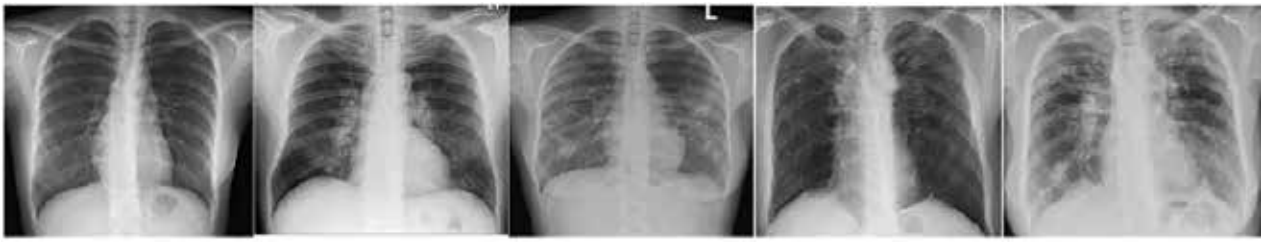
Differential diagnosis of sarcoidosis[22]

Condition	Possible causes
Collagen vascular disease	Systemic lupus erythematosus, Sjögren syndrome, primary biliary cirrhosis, familial granulomatous arthritis
Drug-induced granulomatous disease	Anti-TNF therapy, other biologics, BCG therapy, methotrexate
Environmental/occupational exposure	Beryllium, silica, aluminum, cobalt, talc, titanium, etc; hypersensitivity pneumonitis
Infection	Fungal: histoplasma, blastomyces, coccidioidomyces, cryptococcus, Aspergillus Bacterial: *Brucella*, nontuberculous and tuberculous mycobacteria Parasitic: echinococcus, leishmania, schistosomiasis Viral: HIV
Malignancy	Lymphoma, lung carcinoma, carcinoid tumor, testicular cancer
Vasculitis	Wegener granulomatosis, giant cell arteritis, Takayasu arteritis, Churg Strauss syndrome
Miscellaneous	Crohn disease, common variable immunodeficiency, immune reconstitution inflammatory syndrome

BCG, Bacillus Calmette-Guerin; TNF, tumor necrosis factor.

FIGURE 1

Stages of sarcoidosis on chest x-ray[21,25,32,33]



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From left to right: Scadding stages 0, I, II, III, IV of sarcoidosis on chest x-ray. **Stage 0**: normal. **Stage I**: bilateral hilar adenopathy (frequency, 25%-65%; spontaneous resolution rate, 60%-90%). **Stage II**: bilateral hilar adenopathy and pulmonary infiltrates (frequency, 20%-40%; spontaneous resolution rate, 40%-70%). **Stage III**: pulmonary infiltrates lacking hilar adenopathy (frequency, 10%-15%; spontaneous resolution rate, 10%-20%). **Stage IV**: advanced pulmonary fibrosis (frequency, 5%; spontaneous resolution rate, 0%).

The decision to obtain biopsy samples hinges on the nature of clinical and radiologic findings (**FIGURE 3**).[22,25,26]

Laboratory studies

Multiple abnormalities may be seen in sarcoidosis, and specific lab tests may help support a diagnosis of sarcoidosis or detect organ-specific disease activity (**TABLE 4**).[22,23,25,38] However, no consistently accurate biomarkers exist for use in clinical practice. An angiotensin-converting enzyme (ACE) level greater than 2 times the upper limit of normal may be helpful; however, sensitivity remains low, and genetic polymorphisms can influence the ACE level.[25] Biomarkers sometimes used to assess disease activity are serum interleukin-2 receptor, neopterin, chitotriosidase, lysozyme, KL-6 glycoprotein, and amyloid A.[21]

Additional tests to assess specific features or organ involvement

Pulmonary function testing (PFT) is reviewed in detail below under "pulmonary sarcoidosis."

Electrocardiogram (EKG)/transthoracic echocardiogram (TTE). EKG abnormalities—conduction disturbances, arrhythmias, or nonspecific ST segment and T-wave changes—are the most common nonspecific findings.[30] TTE findings are also nonspecific but

TABLE 3

HRCT findings of sarcoidosis[21,23,25,32]

HRCT findings	Frequency	Description	Location
Potentially reversible			
Lymphadenopathy	80%	Usually nonnecrotic, no mass effect[21,32] Calcified in chronic involvement[21]	Common: bilateral hilar, mediastinal, right paratracheal, subcarinal, aortopulmonary[32]
Nodular and reticulonodular pattern	90% of parenchymal sarcoidosis	< 10 mm irregular nodules in subpleural region along the bronchovascular and perilymphatic distribution[21] Pathognomonic finding: irregular/beaded appearance of vessels, airways, and septa due to these nodules[32] Isolated reticular pattern (rare)	Predominantly in mid and upper lung zones
Ground-glass opacities	16%-83%	Nonspecific feature[32]; might suggest inflammation	
Large nodules Alveolar sarcoidosis Galaxy sign/cluster sign	2.4%-4%	Sarcoid nodules can aggregate into large pulmonary mass with no coalescence in center (cluster sign)[23] Air bronchograms with rarely massive consolidation or cavitation[23,32] Large pulmonary nodule surrounded by many small satellite nodules[23]	
Mosaic attenuation pattern and air trapping		Nonspecific feature which could mean small airway involvement by granulomas or fibrosis	
Mycetoma	2%	Fungal balls can develop in preexisting bullae or cysts[32]	
Pleural effusion Pneumothorax	0.7%-10% 2-3%	Very rare	More often on the right side
Irreversible			
Fibrotic lung disease	5%	Fibrous bands, hilar retraction, traction bronchiectasis, bullae, and irregular reticular opacities, including interlobular lines and irregular septal thickening, architectural distortion, honeycomb cysts[25,32]	Upper and middle lobes; patchy distribution

HRCT, high-resolution computed tomography.

have value in assessing cardiac chamber size and function and myocardial involvement. TTE is indeed the most common screening modality for sarcoidosis-associated pulmonary hypertension (SAPH), which is definitively diagnosed by right heart catheterization (RHC). Further evaluation for cardiac sarcoidosis can be done with cardiac MRI or fluorodeoxyglucose PET in specialized settings.

Lumbar puncture (LP) may reveal lymphocytic infiltration in suspected neurosarcoidosis, but the finding is nonspecific and can reflect infection or malignancy. Oligoclonal bands may also be seen in about one-third of neurosarcoidosis cases, and it is imperative to rule out multiple sclerosis.[28]

Pulmonary sarcoidosis

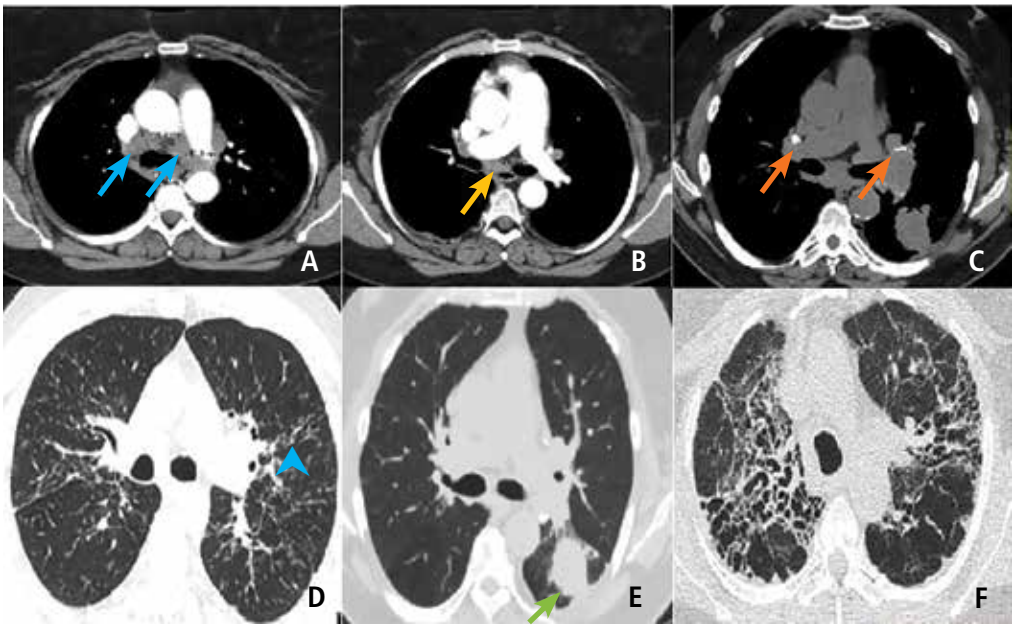
Pulmonary sarcoidosis accounts for most of the morbidity, mortality, and health care use associated with sarcoidosis.[39,40]

Pathology of early and advanced pulmonary sarcoidosis

Sarcoidosis is characterized by coalescing, tightly clustered, nonnecrotizing granulomas in the lung (**FIGURE 4**), most often located along the lymphatic routes of the pleura, in-

FIGURE 2

HRCT findings in sarcoidosis[21,23,25,32]



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Shown here: enlarged lower paratracheal lymph nodes (**A**, blue arrows) and subcarinal nodes (**B**, yellow arrow); calcified bilateral hilar lymph nodes (**C**, orange arrows); multiple nodules along the peribronchovascular bundles (**D**, blue arrowhead shows an example); nodular mass in left lower lobe (**E**, green arrow [biopsy showed noncaseating granuloma with negative cultures]); honeycombing, traction bronchiectasis, and irregular reticulation in a patient with advanced pulmonary sarcoidosis (**F**).

HRCT, high-resolution computed tomography.

terlobular septa, and bronchovascular bundles.[41] Granulomas contain epithelioid cells or multinucleated giant cells surrounded by a chronic lymphocytic infiltrate. Typically, intracytoplasmic inclusions, such as Schaumann bodies, asteroid bodies, and blue bodies of calcium oxalates are noted within giant cells.

In chronic disease, lymphocytic infiltrate vanishes and granulomas tend to become increasingly fibrotic and enlarge to form hyalinized nodules rich with densely eosinophilic collagen. In 10% to 30% of cases, the lungs undergo progressive fibrosis.[40] Nonresolving inflammation appears to be the major cause of fibrosis and the peribronchovascular localization leading to marked bronchial distortion.

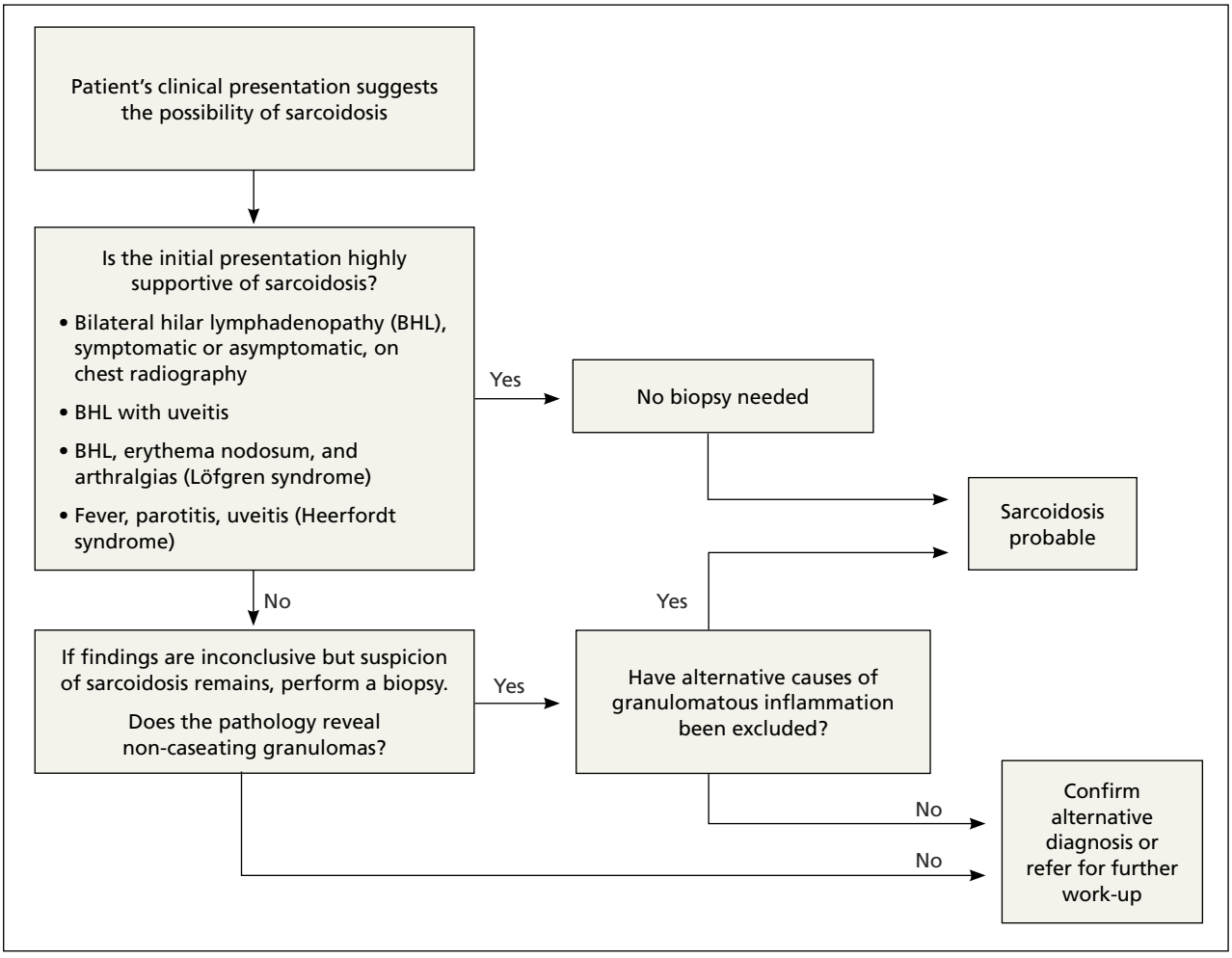
Clinical features, monitoring, and outcomes

Pulmonary involvement occurs in most patients with sarcoidosis, and subclinical pulmonary disease is generally present, even when extrathoracic manifestations predominate.[23] Dry cough, dyspnea, and chest discomfort are the most common symptoms. Chest auscultation is usually unremarkable. Wheezing is more common in those with fibrosis and is attributed to airway-centric fibrosis.[42] There is often a substantial delay between the onset of symptoms and the diagnosis of pulmonary sarcoidosis, as symptoms are nonspecific and might be mistaken for more common pulmonary diseases, such as asthma or chronic bronchitis.[43]

Since sarcoidosis can affect pulmonary parenchyma, interstitium, large and small airways, pulmonary vasculature, and respiratory muscles, the pattern of lung function impairment on PFT varies from normal to obstruction, restriction, isolated diffusion defect, or a combination of these. The typical physiologic abnormality is a restrictive ventilatory defect with a decreased diffusing capacity of the lung for carbon monoxide (DLCO). Extent of disease seen on HRCT

FIGURE 3

Diagnostic algorithm for suspected sarcoidosis[22,25,26]



correlates with level of restriction.[44] Airway obstruction can be multifactorial and due to airway distortion (more likely to occur in fibrotic lung disease) and luminal disease.[45-48] The 6-minute walk test and DLCO can also aid in the diagnosis of SAPH and advanced parenchymal lung disease.

While monitoring is done clinically and with testing (PFT and imaging) as needed, the optimal approach is unclear. Nevertheless, longitudinal monitoring with testing may provide useful management and prognostic information.[40] Pulmonary function can remain stable in fibrotic sarcoidosis over extended periods and actually can improve in some patients.[49] Serial spirometry, particularly forced vital capacity, is the most reliable tool for monitoring; when a decline in measurement occurs, chest radiography can elucidate the mechanism.[50,51]

Because sarcoidosis is a multisystem disease, caution needs to be exercised when evaluating a patient's new or worsening respiratory symptoms to accurately determine the cause of symptoms and direct therapy accordingly. In addition to refractory inflammatory pulmonary disease, airway disease, infection, fibrosis, and SAPH, one needs to consider extrapulmonary involvement or complications such as cardiac or neurologic disease, musculoskeletal disease, depression, or fatigue. Adverse medication effects, deconditioning, or unrelated (or possibly related) disorders (eg pulmonary embolism) may be to blame.

FIGURE 4

Sarcoidosis is characterized by coalescing, tightly clustered, nonnecrotizing granulomas in the affected organ

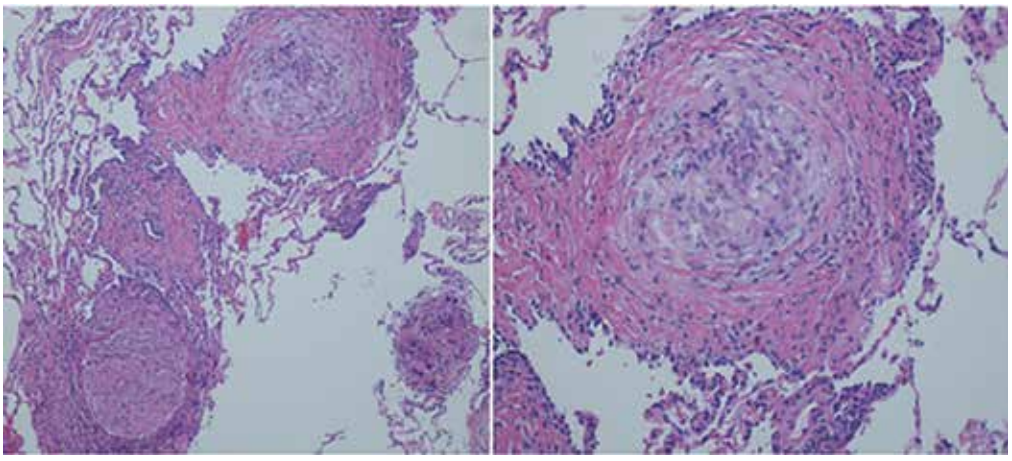


IMAGE COURTESY OF AMANDEEP ANEJA, MD

The panel on the left shows well-formed nonnecrotizing granulomas within the pulmonary interstitium. On high power, nonnecrotizing granuloma with surrounding fibrosis is seen on the right panel.

TABLE 4

Laboratory studies that point to organ/system involvement in sarcoidosis[22,23,25,38]

Laboratory studies	Abnormality	Organ/system involvement
Complete blood count[22,23]	Anemia, leukopenia	Bone marrow, spleen
C-reactive protein[25]	Elevated	Löfgren syndrome, necrotizing sarcoid granuloma
Creatinine	Elevated	Kidney
Calcium[22]	Elevated	Calcium dysregulation
Liver function test[38]	Alkaline phosphatase elevation, transaminitis	Liver
N-terminal pro brain natriuretic peptide (NT-proBNP)[25]	Elevated	Heart, pulmonary hypertension

Determining prognosis

Prognosis of sarcoidosis varies and depends on epidemiologic factors, clinical presentation, and course, as well as specific organ involvement. Patients may develop life-threatening pulmonary, cardiac, or neurologic complications. End-stage disease may require organ transplantation for eligible patients.

Most patients with pulmonary sarcoidosis experience clinical remission with minimal residual organ impairment and a favorable long-term outcome. Advanced pulmonary disease (known as APS) occurs in a small proportion of patients with sarcoidosis but accounts for most of the poor outcomes in sarcoidosis.[40] APS is variably defined, but it generally includes pulmonary fibrosis, SAPH, and respiratory infection.

One percent to 5% of patients with sarcoidosis die from complications, and mortality is higher in women and African Americans.[52] Mortality and morbidity may be increasing.[53] The reasons behind these trends are unclear but could include true increases in disease incidence, better detection rates, greater severity of disease, or an aging population. Increased hospitalizations and health care use might be due to organ damage from granulomatous

TABLE 5

Anti-inflammatory therapy used in sarcoidosis[58,64,67-81]

Drug (usual dose)	Comments	Adverse effects
Corticosteroids (20-40 mg PO daily)[58,64,72,73]	First-line treatment	Diabetes, hypertension, weight gain, bone loss, cataracts, glaucoma, infection
Methotrexate (5-15 mg PO/SQ weekly)[67]	First choice for second-line treatment of sarcoidosis	Bone marrow suppression, kidney failure, hepatotoxicity, pneumonitis, gastrointestinal toxicity, lymphoma
Azathioprine (50-200 mg PO daily)[68]	Similar efficacy as methotrexate, but increased risk of infection	Leukopenia, nausea, infection
Mycophenolate mofetil (500-3000 mg PO daily)[74,75]	More effective than other antimetabolites for treatment of chronic ocular inflammation Can be used in patients with kidney dysfunction	Nausea, diarrhea, opportunistic infection
Leflunomide (10-20 mg PO daily)[69,76]	Synergistic effect with methotrexate Less effective for musculoskeletal and neurologic involvement Effective for cutaneous, ocular, and sinonasal involvement	Leukopenia, hepatotoxic effects, infection, alopecia
TNF-alpha inhibitors: infliximab, adalimumab[70,71,76,77]	Third-line treatment indications: • failed treatment with steroids and antimetabolites • chronic pulmonary disease with decreased FVC and FEV_1 • lupus pernio • neuro- and cardiac sarcoidosis	Injection site reaction, neutropenia, TB reactivation, infection, sarcoid-like granulomatosis, heart failure, and demyelinating disease
Rituximab[78,79]	Has shown effectiveness in ocular sarcoidosis	HBV reactivation, multifocal leukoencephalopathy, peripheral edema, rash, angioedema, hepatotoxicity, neuropathy
Levofloxacin, ethambutol, azithromycin, and rifampin (CLEAR)[80,81]	Persistent cutaneous and pulmonary sarcoidosis	Leukopenia, arthralgia, insomnia, rash

CLEAR, concomitant levofloxacin, ethambutol, azithromycin, and rifampin regimen; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HBV, hepatitis B virus; TB, tuberculosis.

inflammation (and resultant fibrosis), complications associated with treatment, and psychosocial effects of the disease/treatment.

Management

Management consists primarily of anti-inflammatory or immunosuppressive therapies but can also include measures to address specific complications (such as fatigue) and organ transplant, as well as efforts to counter adverse medication effects. Other supportive and preventive measures may include, on a case-by-case basis, oxygen supplementation, vaccinations, or pulmonary rehabilitation. Details of these are found in other, more in-depth reviews on treatment; we will briefly review anti-inflammatory therapy, which forms the cornerstone of treatment in most patients with sarcoidosis.

General approach to treatment decisions. Anti-inflammatory therapy is used to reduce granulomatous inflammation, thereby preserving organ function and reducing symptoms. A decision to begin treatment is one shared with the patient and is based on symptoms and potential danger of organ system failure.[54] Patients who are symptomatic or have progressive disease or physiologic impairment are generally candidates for

treatment. Monitoring usually suffices for those who have minimal symptoms, stable disease, and preserved organ function.

Patients with pulmonary sarcoidosis at CXR stage 0 should not receive treatment, given that large, randomized trials have shown no meaningful benefit and that these patients have a high likelihood of spontaneous remission and excellent long-term prognosis.[55-58] However, a subgroup of patients classified as stage 0/I on CXR may show parenchymal disease on HRCT,[59] and, if more symptomatic, could be considered for treatment. For patients with stage II to IV pulmonary sarcoidosis with symptoms, there is good evidence that treatment may improve lung function and reduce dyspnea and fatigue.[57,60-62]

Corticosteroids are first-line treatment for most patients. Based on expert opinion, treatment of pulmonary sarcoidosis is generally started with oral prednisone (or an equivalent corticosteroid). A starting dose of 20 to 40 mg/d generally is sufficient for most patients. If the patient responds to initial treatment, prednisone dose is tapered over a period of months. If symptoms worsen during tapering, the minimum effective dose is maintained without further attempts at tapering. Treatment is continued for at least 3 to 6 months but it might be needed for longer durations; unfortunately, evidence-based guidelines are lacking.[63] Once the patient goes into remission, close monitoring is done for possible relapses. Inhaled corticosteroids alone have not reduced symptoms or improved lung function in patients with pulmonary sarcoidosis.[64-66]

Steroid-sparing agents are added for many patients. For patients receiving chronic prednisone therapy (≥ 10 mg for > 6 months), steroid-sparing agents are considered to minimize the adverse effects of steroids or to better control the inflammatory activity of sarcoidosis. These agents must be carefully selected, and clinical and laboratory monitoring need to be done throughout therapy. **TABLE 5**[58,64,67-81] shows the major anti-inflammatory treatment agents used for sarcoidosis.

The management might be complicated for extrapulmonary, multi-organ, and advanced sarcoidosis (advanced pulmonary sarcoidosis, cardiac disease, neurosarcoidosis, lupus pernio, etc) when specialized testing, as well as a combination of corticosteroids and steroid-sparing agents (with higher doses or prolonged courses), might be needed. This should be performed at an expert sarcoidosis center, ideally in a multidisciplinary setting involving pulmonologists and/or rheumatologists, chest radiologists, and specialists as indicated, based on specific organ involvement.

Research and future directions

Key goals for research are identifying more accurate biomarkers of disease, improving diagnosis of multi-organ disease, determining validated endpoints of clinical trials in sarcoidosis, and developing treatments for refractory cases.

There is optimism and opportunity in the field of sarcoidosis overall. An example of an advancement is in the area of APS, as the severity and importance of this phenotype has been better understood. Worldwide registries and trials of pulmonary vasodilator therapy (bosentan, sildenafil, epoprostenol, and inhaled iloprost) in patients with SAPH without left ventricular dysfunction are promising.[82-85] However, no benefit in survival has been shown.

RioSAPH is a double-blind, placebo-controlled trial of Riociguat (a stimulator of soluble guanylate cyclase) for SAPH (NCT02625558) that is closed to enrollment and undergoing data review. Similarly, results of the phase IV study of pirfenidone, an antifibrotic agent that was shown to decrease disease progression and deaths in idiopathic pulmonary fibrosis,[86] are awaited in the near future.

Other potential directions being explored are multicenter patient registries and randomized controlled trials, analyses of existing databases, use of biobanking, and patient-centered outcome measures. Hopefully, the care of patients with sarcoidosis will become more evidence based with ongoing and upcoming research in this field. JFP

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