Sarcoidosis is a multisystemic disease characterized by frequent remissions and exacerbations, with multiple pulmonary and extrapulmonary symptoms that may be difficult to assess and manage, and without a treatment armamentarium that can sufficiently alter the course of the disease. The health-related quality of life of individuals suffering from sarcoidosis matches that of patients with symptomatic AIDS or end-stage renal disease, with significant decrements in physical, emotional, and social functioning [1]. Many cases of sarcoidosis are diagnosed and managed by primary care providers. It is increasingly important for physicians to accurately diagnose, assess, and treat based on a patient’s specific symptoms and psychosocial needs.

CASE STUDY

Initial Presentation

A 40-year-old African-American woman presents to her primary care physician with complaints of mild dyspnea on exertion and occasional dry cough of approximately 3 months’ duration.

- When should a diagnosis of sarcoidosis be suspected?

While sarcoidosis occurs worldwide and may affect any individual, the majority of patients are diagnosed between age 20 to 40 years. In the United States, African-American women are most commonly affected [2]. A subanalysis of symptomatic patients in the ACCESS study (A Case-Control Etiologic Sarcoidosis Study) demonstrated that pulmonary symptoms were the presenting complaint in just over one half of patients, with sole pulmonary complaints present in half of this group [2]. Skin manifestations were present in 24%, and systemic symptoms were present in 12% of patients. The presence of pulmonary symptoms actually resulted in a delay between the time of initial presentation and diagnosis. This finding may be due to the consideration of more commonly seen alternative diagnoses presenting with similar symptoms, such as asthma or bronchitis [3].

Throughout their clinical course, almost all cases of sarcoidosis are marked by pulmonary involvement. Patients may complain of a dry cough, a vague diffuse chest discomfort, and shortness of breath, particularly with exertion.

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Pleuritic chest pain is uncommon. Although airflow obstruction on pulmonary function testing is relatively common, only up to 10% of patients manifest endobronchial granulomata resulting in symptoms such as wheezing or stridor and occasionally, atelectasis [4].

Constitutional symptoms such as fever, night sweats, fatigue, malaise, and weight loss may occur in up to one third of patients with sarcoidosis. Polyarthralgias are common, particularly at presentation. Sarcoidosis may affect any organ system. The most common organs involved include the skin (30%), eyes (25%), and liver and spleen (20%). Abnormalities in calcium metabolism (hypercalcuria followed by hypercalcemia) are detected in about 15% of patients. Clinically apparent cardiac and nervous system involvement occurs in about 5% of patients [2].

Further History

The patient had been well, with unlimited exercise tolerance, until 4 months earlier when she developed dyspnea with strenuous exercise and a dry cough unrelated to meals or lying flat. She is a homemaker. She has a 10-year history of cigarette smoking but quit smoking 6 years ago. There is no history of illicit drug use, known exposures, or recent travel. There is no family history of lung disease.

- Are there any particular risk factors to identify when considering a diagnosis of sarcoidosis?

A large case-control study of patients involved in the ACCESS trial attempted to identify work-related exposures as a possible cause of sarcoidosis. Although the analysis did not reveal any particular occupation to be singularly responsible for a diagnosis of sarcoidosis, there were several associations made with increased risk, including working with building materials, hardware, or industrial organic dusts [5,6]. Further data indicates that sarcoidosis aggregates in families. For African Americans, the familial relative risk estimate for a sarcoidosis history in a parent or sibling was 3.1. The relative risk in white parents and siblings was 16.6, although a fairly wide confidence interval made it more difficult to interpret these data [7]. To date, no clear association has been established between smoking as a risk factor and the development of sarcoidosis. [8]

- What is the recommended evaluation of patients with suspected sarcoidosis?

There are 3 primary objectives to consider when evaluating a patient with possible sarcoidosis: (1) to assess which organs are involved and to what extent they are involved, (2) to assess whether the disease is stable or progressing, and (3) to determine if therapy will benefit the patient. Thus, the workup should include a thorough history and physical examination with emphasis on pulmonary, dermatologic, ocular, hepatic, and cardiovascular abnormalities.

Chest auscultation may reveal fine, late, or mid-expiratory crackles but comparatively less than what may be heard in pulmonary fibrosis. Chest radiograph should be performed in suspected sarcoidosis, as pulmonary sarcoidosis is classified according to chest radiographic findings [9]:

- Stage 0: Absence of radiographic abnormalities
- Stage 1: Bilateral hilar and/or mediastinal adenopathy without pulmonary parenchymal abnormalities
- Stage 2: Hilar and/or mediastinal lymphadenopathy with pulmonary parenchymal abnormalities (generally a diffuse interstitial pattern)
- Stage 3: Diffuse parenchymal disease without nodal enlargement
- Stage 4: Pulmonary fibrosis with evidence of volume loss, cystic or honeycomb changes

A stage 2 chest x-ray with evidence of intrathoracic lymphadenopathy is the most commonly encountered radiographic finding, occurring in 85% of patients, and is typically bilateral hilar lymphadenopathy with right paratracheal lymphadenopathy. The pulmonary parenchymal changes of sarcoidosis have a strong predilection towards the upper lung fields, unlike those noted in other diffuse parenchymal diseases such as pulmonary fibrosis, which is basilar predominant. High-resolution computed tomography scan typically demonstrates multiple small nodules in a perivascular distribution, along with thickened bronchovascular bundles and interlobular septa. Evidence of mediastinal lymphadenopathy and nodular lesions mimic other conditions including eosinophilic granuloma, lymphoma, or metastatic disease [10].

Pulmonary function testing including spirometry with bronchodilator, lung volumes, and diffusing capacity of carbon monoxide (DLCO) is often helpful in evaluating sarcoidosis. The 2 most common abnormalities seen on pulmonary function testing are reductions in lung volume and vital capacity, representing a restrictive ventilatory defect, and a reduction in DLCO. Obstructive ventilatory defects may also be seen in up to 30% of nonsmokers with sarcoidosis and are believed to represent endobronchial involvement [11].
Cutaneous involvement is one of the most common manifestations of extrapulmonary sarcoidosis. Erythema nodosum is the most common nonspecific cutaneous lesion and usually manifests as extremely tender, subcutaneous nodules, often on anterior tibia. Onset of erythema nodosum is often sudden and accompanied by systemic symptoms such as fever, malaise, and polyarthralgias. Lofgren’s syndrome refers to the constellation of erythema nodosum, bilateral hilar adenopathy, and polyarthralgias, which represents an acute presentation of systemic sarcoidosis [12].

The most common ocular manifestations of sarcoidosis are uveitis and conjunctival nodules. However, lacrimal gland involvement is also relatively common as well as asymptomatic. No specific extraocular manifestations of sarcoid have been associated with the development of ocular involvement. A dilated funduscopic examination by an ophthalmologist is recommended to best identify ocular disease [13].

Liver function tests should be obtained to assess hepatic involvement. The spectrum of disease in liver is also wide and ranges from asymptomatic liver dysfunction, chronic cholestasis, portal hypertension, cirrhosis, and nodular regenerative hyperplasia. Once again, no specific relationship to disease presence or severity at other sites has been established [14].

An electrocardiogram should be performed on all patients with suspected sarcoidosis. Conduction abnormalities ranging from first-degree AV block to complete heart block are some of the most common cardiac abnormalities. Complete heart block occurs in approximately 30% of patients, of which a vast majority had episodes of syncope. Cardiac manifestations may also include mitral regurgitation, congestive heart failure, ventricular aneurysms, pericardial effusions and tamponade, pericarditis, ventricular arrhythmias, and sudden death [15].

Serum angiotensin-converting enzyme level, while not useful in diagnosis because of its poor specificity, may be useful in judging compliance with therapy in patients with an elevated level prior to treatment [16].

Further History

A chest radiograph reveals evidence of mediastinal lymphadenopathy and parenchymal interstitial changes. Pulmonary function testing shows diminished vital capacity and DLCO.

1. Which patients are most likely to benefit from oral corticosteroids?

Sarcoidosis is often a mild, self-limited disease and frequently does not require treatment. When treatment is required, corticosteroids are the first line of therapy. Although corticosteroids have been shown to improve symptoms and may correct laboratory, radiographic, or pulmonary function abnormalities, no current evidence demonstrates that corticosteroids significantly alter the natural history of the disease.

Oral corticosteroid therapy should be strongly considered in the following situations [9]:

1. Hypercalcemia or hypercalcuria
2. Central nervous system involvement
3. Posterior uveitis
4. Active cardiac involvement
5. Progressive involvement in any organ system, ie, progressive respiratory symptoms, evidence of abnormal pulmonary function parameters such as reduced diffusion or vital capacity, or persistent radiographic abnormalities.

In addition, an elevated serum calcium level is often seen in the setting of sarcoidosis and may require treatment.

- What is the optimal dose and duration of corticosteroid therapy?

The optimal dose and duration of corticosteroids has not been determined in randomized trials. The treatment regimen is individualized based on symptoms and response rate. For pulmonary sarcoidosis, the initial dose is generally 30 to 40 mg per day of prednisone, observing for either symptomatic or radiographic response or improvement in pulmonary function parameters at 1 to 3 months. Patients who fail to respond to an initial 3-month course are unlikely to respond to a more prolonged course of therapy. Among responders, the prednisone dose may be slowly tapered to 10 to 20 mg per day, but treatment should be continued for a minimum of 9 to 12 months. Reappearance of symptoms or radiographic abnormalities occurs frequently after discontinuation of treatment. Some studies have found that more than one third of patients experience recurrence of symptoms within 2 years of discontinuation of therapy [17].

- What additional therapies may be offered to patients with sarcoidosis?

The antimalarial drug hydroxychloroquine may have steroid-sparing effects and is particularly useful for neurosarcoidosis, skin involvement, and abnormalities in calcium...
metabolism. It should not be used in patients with posterior uveitis, since retinitis is a potential toxic effect. Cytotoxic agents such as azathioprine, methotrexate, and cyclophosphamide have all been used in the treatment of sarcoidosis. Although these agents are clearly of value in selected patients, there are no studies that clearly delineate when these drugs should be used for therapy [18]. Lung transplantation is an additional therapeutic option.

**What is the natural history and prognosis of isolated pulmonary sarcoidosis?**

The prognosis of patients with isolated pulmonary sarcoidosis is generally good. A majority of these patients undergo spontaneous remission or stabilization of disease within 2 to 5 years of diagnosis. Patients with stage 1 chest x-rays have a greater than 80% rate of radiographic resolution compared with patients with stage 2 (60%) or stage 3 (30%) findings. A small number of patients may progress to end-stage lung disease. In general, patients who present with extrapulmonary disease have a worse prognosis [19].

**When should a patient with sarcoidosis be referred for lung transplantation?**

Only patients with severe physiologic impairment refractory to medical therapy should be considered for lung transplantation. A recent multicenter study of sarcoidosis patients on lung transplant waiting lists indicated that 27% of patients die prior to transplantation. There was no significant difference between pulmonary function testing parameters in survivors and nonsurvivors, however the presence of underlying pulmonary hypertension, the amount of supplemental oxygen required, and African-American race were significant predictors of mortality [20]. At present, there are no well-defined guidelines for referral of sarcoidosis patients. However, extrapolation from pulmonary fibrosis waiting list mortality suggests the following are reasonable referral guidelines: (1) a forced vital capacity less than 60% predicted, (2) resting hypoxemia, (3) failure to maintain lung function despite treatment with steroids or other immunosuppressive agents, or (4) the presence of pulmonary hypertension.

**SUMMARY**

Because sarcoidosis has many and protean manifestations, it may often be difficult to diagnose. In addition, deciding on a course of treatment can be difficult in patients whose symptoms are quiescent or slowly progressive. Due to the multisystemic nature of the disease, sarcoidosis may considerably and adversely affect the quality of life of patients afflicted. One study revealed that 60% of patients reported symptoms of clinical depression. A patient’s insurance status, income, and access to medical care were all highly correlated with depressive symptoms [21]. Additional studies have indicated that patients with sarcoidosis report poor quality of life, worsened when they are on corticosteroid therapy. Of note, experienced physicians were not able to adequately assess particular sarcoid-related symptoms. This highlights the need for improved communication between physicians and patients with sarcoidosis, who may have multiple occult manifestations that may impact their quality of life, including stress, fatigue, pain, and sleep disturbances [1,8].

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**References**

Sarcoidosis


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CME EVALUATION: The Diagnosis and Management of Sarcoidosis

DIRECTIONS: Each of the questions below is followed by several possible answers. Select the ONE lettered answer that is BEST in each case and circle the corresponding letter on the answer sheet.

1. Which of the following is NOT a common finding in sarcoidosis?
   (A) Pulmonary involvement
   (B) Pleuritic chest pain
   (C) Skin manifestations
   (D) Depression

2. Which of the following tests is NOT useful in diagnosing sarcoidosis?
   (A) Electrocardiogram
   (B) Serum angiotensin-converting enzyme levels
   (C) Spirometry
   (D) Liver enzymes

3. The rate of radiographic resolution in patients with stage 1 chest x-ray is
   (A) 80%
   (B) 70%
   (C) 60%
   (D) 30%

4. Which of the following statements regarding corticosteroid therapy (CT) in sarcoidosis is FALSE?
   (A) Patient quality of life may worsen while on CT
   (B) CT has been shown to improve pulmonary function abnormalities
   (C) CT is contraindicated in the setting of hypercalcemia
   (D) CT should be strongly considered in the setting of posterior uveitis

5. Other agents used to treat sarcoidosis include
   (A) Hydroxychloroquine
   (B) High-dose vitamin D
   (C) Cyclophosphamide
   (D) Methotrexate
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