CLINICAL VIGNETTE

A Curious Case of a Cough

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Case Presentation

A 35-year-old male with no chronic medical problems, presented to pulmonary with intermittent cough, and shortness of breath with exertion. He reported no difficulty when walking at a slow pace, but dyspnea and cough as his pace increased. The dry cough occurred intermittently, mostly with exertion. He denied dysphagia, odynophagia, chest pain, palpitations, hemoptysis, fever, chills, weight loss, recent travel, or putrid sputum production. He was a lifelong nonsmoker, owned a dog, and worked as a police officer without any occupational exposures. His vital signs were unremarkable and physical exam was normal, revealing no stridor, wheezing, or abnormal lymphadenopathy. Pulmonary function studies were normal without obstruction or restriction. Computer tomography of the chest revealed multicompartmental calcified and noncalcified lymphadenopathy and multiple scattered calcified and non-calcified pulmonary parenchymal nodules and masses. The largest was within the right upper lobe, measuring 37 x 25 mm. Computed tomography (CT) guided lung biopsy of right upper lobe revealed non-necrotizing granulomas, negative for mycobacteria, concerning for pulmonary sarcoidosis.

Discussion

Introduction: Sarcoidosis is a systemic granulomatous disease characterized by noncaseating granulomas in involved organs. The etiology of Sarcoidosis remains unknown. The prevalence of Sarcoidosis is not known with certainty, but estimated to be about 10 to 20 per 100,000 population, with blacks having a lifetime risk of 2.4 percent compared to 0.85 percent in whites.[1,2] Sarcoidosis typically affects younger adults between 20 and 60 years of age.[3] Disease often is detected incidentally on imaging prior to development of symptoms.

Clinical Manifestations: Lung involvement occurs in about 90 percent of patients with sarcoidosis.[4] However, about 30 percent of patients present with extrathoracic involvement,[4-6] such as skin (16%), lymph node (15%), eye (11%), liver (11%), neurologic (4.5%), parotid (4%), bone marrow (4%), ENT (3%), cardiac (2%), renal (0.7%), bone/joint (0.5), and muscle (0.4%).[4]

Symptoms of pulmonary sarcoidosis include cough, dyspnea, chest pain, fatigue, malaise, fever, weight loss.[7] Extrapulmonary sarcoidosis symptoms are dependent on the organ involved, and may include skin lesions, visual changes, dry eyes or mouth, parotid swelling, palpitations, syncope, joint pain or swelling, and muscle weakness.

Laboratory Evaluation: Regular laboratory evaluation is advised, including complete blood count and differential, liver function tests, blood urea nitrogen, creatinine, electrolytes, glucose, calcium.[8] Serum angiotensin converting enzyme (ACE) has been evaluated for its potential role in the diagnosis or monitoring of disease, but without clear evidence of benefit.[9] Although ACE level is elevated in about 75 percent of patients with untreated sarcoidosis, its utility as a diagnostic test is limited due to poor sensitivity and specificity.[10]

Pulmonary imaging is essential in the diagnosis of sarcoidosis as lung involvement occurs in over 90 percent of patients with sarcoidosis. Imaging should start with chest radiograph, followed by high resolution computed tomography. Sarcoidosis is staged radiographically based on chest radiograph (Figure 1).[11]

High resolution CT scan (HRCT): Obtained to evaluate abnormalities on chest radiograph, HRCT can more clearly evaluate the lung parenchyma and mediastinum, and identify abnormalities not seen on chest radiograph. Findings typically seen on HRCT scan include hilar and mediastinal lymphadenopathy, thickening of bronchovascular bundles, ground glass opacification, bronchial wall thickening, fibrosis, traction bronchiectasis, cavities, cysts.[12-14]

Diagnosis: Sarcoidosis is diagnosed based on compatible clinical and radiographic manifestations, exclusion of other diseases, and histopathology of noncaseating granulomas. Biopsy should be performed of the most accessible lesions including cutaneous lesions, subcutaneous nodules, conjunctival lesions, or parotid glands.[11] If accessible lesions are not apparent, bronchoscopy with biopsy of enlarged lymph nodes or lung parenchyma is performed. Bronchoscopy is performed with bronchoalveolar lavage, endobronchial biopsy, transbronchial lung biopsy, and endoscopic ultrasound guided needle aspiration. Bronchoalveolar lavage can assist in the diagnosis of sarcoidosis by demonstrating a reduced number of CD8 cells, elevated CD4 to CD8 ratio, increased activated T cells, and exclusion of infections and malignancy as alternative diagnoses.[11] Endobronchial biopsies are frequently positive and may increase the diagnostic yield compared to transbronchial biopsies alone as approximately 70% of patients with

stages II and III disease have endobronchial disease.[15,16] Transbronchial lung biopsy has a yield of about 50 to 75% among patients with lung parenchymal findings.[17] Endoscopic ultrasound guided needle aspiration (TBNA) is done to obtain core biopsy tissue from intrathoracic lymph nodes and has a diagnostic yield of approximately 80 to 90%.[11] The triad of CD4 to CD8 ratio greater than four to one, a lymphocyte percentage greater than or equal to 16% on bronchoalveolar lavage, and transbronchial biopsy demonstrating noncaseating granulomas was most specific for sarcoidosis.[18]

Histopathology*:* The characteristic feature of sarcoidosis is noncaseating granuloma, a chronic inflammatory reaction formed by the accumulation of epithelial cells, monocytes, lymphocytes, macrophages, and fibroblasts.[19] Multinucleated giant cells are frequently found among the epithelioid cells within the granuloma and have cytoplasmic inclusions such as asteroid bodies, Schaumann bodies, and birefringent crystalline particles.[20,21]

Differential Diagnosis: It is essential to exclude alternative possibilities in the diagnosis of sarcoidosis. Diseases other than sarcoidosis that may present with granulomatous lung inflammation include: mycobacterial and fungal infections, hypersensitivity pneumonitis, pneumoconiosis such as chronic beryllium disease, drug-induced hypersensitivity, pulmonary Langerhans cell histiocytosis, foreign body granulomatosis, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, bronchocentric granulomatosis, and primary immunodeficiencies.[11] Sarcoid-like histopathology can also be seen in lymph nodes from patients with malignancies such as lymphoproliferative disorders, germ cell testicular tumors, breast cancer, renal cell carcinoma, and leiomyosarcoma, among others.[22-25] Caution is therefore advised when making the diagnosis of sarcoidosis based solely on lymph node histopathology, but without other typical features of sarcoidosis.

Assessment for extrapulmonary disease: As sarcoidosis can involve multiple organ systems, once the diagnosis of pulmonary sarcoidosis is confirmed the extent of involvement of other organs should be evaluated. Patients should undergo skin exam to evaluate for lupus pernio and erythema nodosum, ophthalmologic examination to evaluate for uveitis and optic neuritis, electrocardiogram to evaluate for heart block and arrhythmias, and spot urine for calcium and creatinine to assess for hypercalcemia and hypercalciuria. Further cardiac and neurologic imaging should be performed based on signs and symptoms.[11]

Treatment of Pulmonary Sarcoidosis: Therapy for pulmonary sarcoidosis is aimed at reducing granulomatous inflammation and preventing the development of fibrotic lung disease. Many patients with pulmonary sarcoid do not require treatment as they may have nonprogressive disease or spontaneous remission. Patients who are asymptomatic with stage I radiographic changes may be observed without therapy as about 60 to 80 percent have spontaneous remission.[26] Asymptomatic stage II radiographic patients with normal or mildly abnormal lung function, can be followed closely with PFTs for three to six months to identify progression, without the initiation of treatment. About 50 percent of untreated stage II radiographic changes will have resolution by 36 months.[26] Asymptomatic stage III radiographic disease with normal or mildly abnormal lung function may be followed untreated closely with PFTs for 3 to 6months, however only about 33 percent will have spontaneous resolution and the majority will need treatment.[26]

Indications for treatment is a combination of:[26-28]

- Progressive pulmonary symptoms (cough, shortness of breath)
- Fall in lung function of one of more of following (decline in total lung capacity (TLC) of 10percent or more, fall in forced vital capacity (FVC) of 15percent or more, decrease in diffusing capacity (DLCO) of 20 percent or more, oxygen desaturation of 4% or more)
- Progressive radiographic changes

Initial therapy consists of oral glucocorticoid 0.3 to 0.6mg/kg ideal body weight for about 6 weeks, with taper of 5 to 10mg decrements every 4 to 12 weeks.[27,29] Maintenance doses are usually in the range of 0.25 to 0.4mg/kg per day. Given recurrence of symptoms are common, maintenance doses are continued for three to six months, giving a total treatment period of approximately one year.[30] About one third of patients will relapse after discontinuation of steroids and require another course of therapy, with a small number requiring more long-term or indefinite maintenance therapy to control their symptoms.[31,32] Favorable response to glucocorticoid therapy is defined by improvement in symptoms, improvement or resolution of radiographic abnormalities, and physiologic improvement in pulmonary function tests or oxygen saturation.[32] A relapse is defined as worsening of symptoms, progressive radiographic opacities, and decline of 10 percent or more in FVC or TLC.[32]

While most patients respond to glucocorticoid therapy, some patients do not despite an adequate trial, and may require intensification of therapy with immunosuppressive agents such as methotrexate, azathioprine, leflunomide, or tumor necrosis factor-alpha inhibitors.

Case Outcome

Patient was treated with glucocorticoid 0.6mg/kg ideal body weight for 6 weeks with improvement in his symptoms of cough and shortness of breath. PFTs which were normal previously were unchanged, and chest imaging was unchanged. Glucocorticoids were tapered and stopped after a total treatment duration of 12 months. The patient remained asymptomatic off steroids without relapse of cough and shortness of breath. Chest imaging remained stable without progression of disease.

Figures

Stage	Chest radiographic findings	Natural history
Stage I	Bilateral hilar adenopathy + right paratracheal node enlargement	75 percent of patients show regression of hilar nodes within one to three years
Stage II	Bilateral hilar adenopathy + upper zone predominant reticular opacities	Two-thirds of patients undergo spontaneous resolution. Remainder of patients have stable or progressive disease
Stage III	Upper zone predominant reticular opacities, with shrinking hilar nodes	Approximately 33 percent of patients show spontaneous disease resolution after 5years. Majority of patients require treatment.
Stage IV	Upper zone predominant reticular opacities. May also include conglomerated masses, traction bronchiectasis, calcification, cavitation, cyst formation	Non-resolving, and progressive
Nodular Sarcoid	Multiple, bilateral lung nodules and minimal hilar adenopathy	Non-resolving, and progressive

Figure 1: Radiographic stages and natural history of pulmonary sarcoid

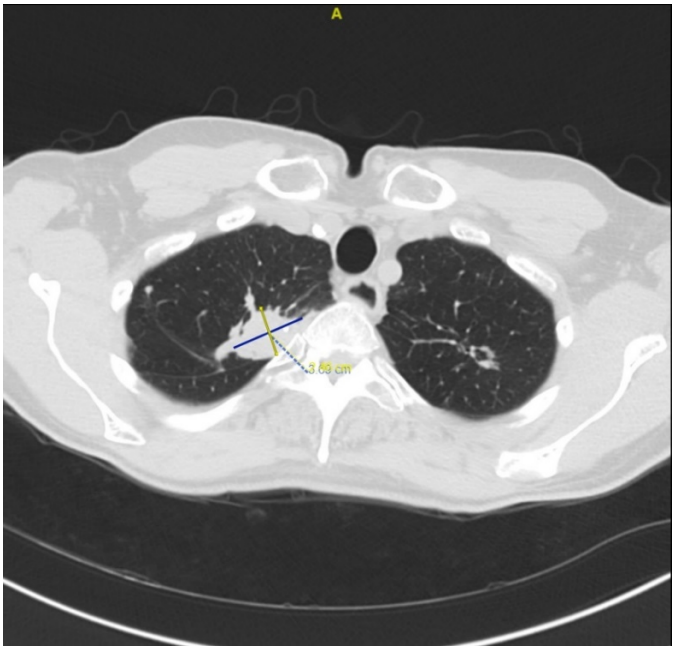

Figure 2: Computer tomography of the lungs showing right upper lobe mass measuring 37 x 25 mm

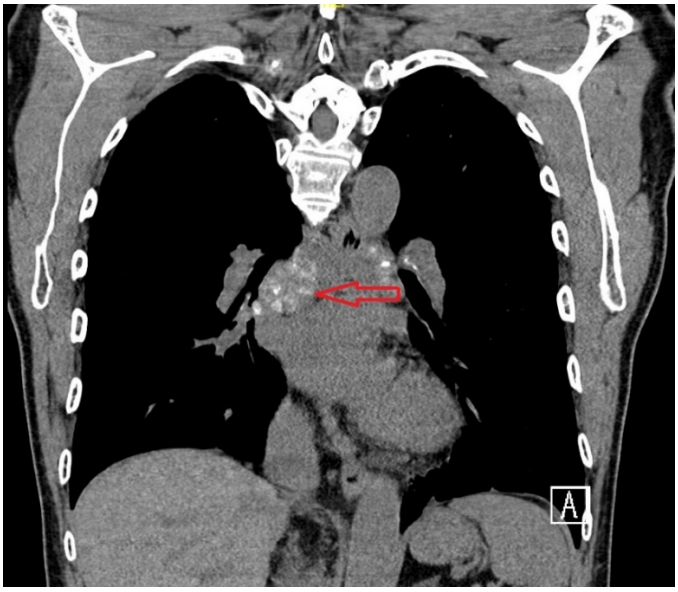

Figure 3: Computer tomography of the lungs showing calcified and noncalcified lymphadenopathy (red arrow)

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