CASE REPORT

A 50-Year-Old Man with Stage 2 Sarcoidosis with Pleural Involvement

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We present a case of a 50-year-old man who presented with progressive shortness of breath, cough, chest pain, and weight loss. His computer tomography (CT) scan of the chest showed a left-sided pleural effusion, subpleural and peribronchovascular nodules, bilateral hilar and mediastinal lymphadenopaties. Traasbronchial biopsies of the lung parenchyma and Video-Assisted Thoracoscopic Surgery (VATS) with pleural biopsies revealed the presence of noncaseating granulomas. A diagnosis of stage 2 sarcoidosis with pleural involvement was made and treatment with prednisone was started. The patient continued with persistent dyspnea and a left-sided pleural effusion. Steroid treatment was tapered and leflunomide therapy was initiated. A significant improvement of his clinical condition was seen after 1 month on treatment.

KEYWORDS: chest pain, interstitial lung disease, pleural disease (effusion, pneumothorax).

A 50-year-old man presented to the emergency department with progressive shortness of breath for 6 months. He described a dry cough, left-sided chest pain, malaise, night sweats, and a 15-pound weight loss. The patient had never smoked cigarettes, but he had been exposed to asbestos and wood dust when working at a sawmill. His physical examination was remarkable for decreased breath sounds at the left lung base. The admission blood tests were within normal limits. Chest radiography and a computed tomography (CT) scan of the chest were performed (the CT scan is shown in Figures 1 and 2). The CT scan showed a left pleural effusion with subpleural and peribronchovascular nodules. Also demonstrated on the CT scan were bilateral hilar and mediastinal lymphadenopathies with faint central calcification. As the left-sided pleural effusion was initially suspected to be malignant, a thoracentesis was performed, and it revealed an exudative effusion. The total white cell count in fluid was 2100/μL (lymphocytes, 76%), and cultures for aerobic and anaerobic bacteria, acid fasting bacilli, and fungi were negative. Cytology was negative for malignant cells. On the basis of the findings in the lung parenchyma and the presence of mediastinal lymphadenopathies, fiberoptic bronchoscopy with bronchoalveolar lavage, protected specimen brushing, transbronchial needle aspiration, and transbronchial biopsies were performed. Mediastinal lymph node cytology was negative for malignant cells, whereas transbronchial biopsies showed noncaseating granulomas (Figure 3). At that time, our differential diagnoses of noncaseating granulomas included mycobacterium infection (although this usually presents caseating granulomas), berylliosis, histoplasmosis, and sarcoidosis. The tuberculin skin test (purified protein derivative) and serology for human immunodeficiency virus were negative. Bronchoalveolar lavage and cultures of lung tissue biopsies as well as needle aspiration from mediastinal lymph nodes were negative for mycobacterial, fungal, and bacterial organisms. The beryllium lymphocyte proliferation test was normal. Serologic antibodies for *Aspergillus*, *Blastomyces*, *Coccidioides*, and *Histoplasma* were negative. The urinary *Histoplasma* antigen was negative as well. The Department of Infectious Diseases was consulted, and an empirical treatment for histoplasmosis with itraconazole was started on the basis of the residence of the patient and the presence of noncaseating granulomas. After 1 month of antifungal treatment, there was no significant improvement. Video-assisted thoracoscopic surgery with pleural biopsy was performed because of persistent pleural effusion and concern about an underlying infectious or malignant process. Pleural biopsies showed noncaseating granulomas (Figure 4). Pleural fluid was sent for adenosine deaminase (17 U/L) and flow cytometry (CD4/CD8 2.71). Cultures and cytology remained negative. A diagnosis of stage 2 sarcoidosis with pleural involvement was made, and treatment with prednisone was started.

Discussion

The overall prevalence of pleural involvement in sarcoidosis is about 3%. Patients with pleural sarcoidosis tend to be between 30 and 50 years of age, in contrast to the usual presentation of sarcoidosis between 20 and 30 years of age. The most common forms of pleural involvement are pleural effusions, pneumothorax, pleural thickening, and pleural nodules.[1] Most effusions are usually small or modest in size, with few reports describing massive effusions.[2] Recurrent pleural and pericardial effusions due to sarcoidosis have been reported as well.[3] The fluid is typically a lymphocytic exudate, and almost all cases describe a CD4 predominant lymphocytic effusion with CD4/CD8 ratios ranging from 2.35 to 8.6.[1] The presence of bloody pleural effusions in sarcoidosis most likely represents the rupture of small vessels that are compressed or infiltrated by granulomas.[4]

The majority of patients with reported sarcoid pleural effusions have stage 2 disease. With the progression of

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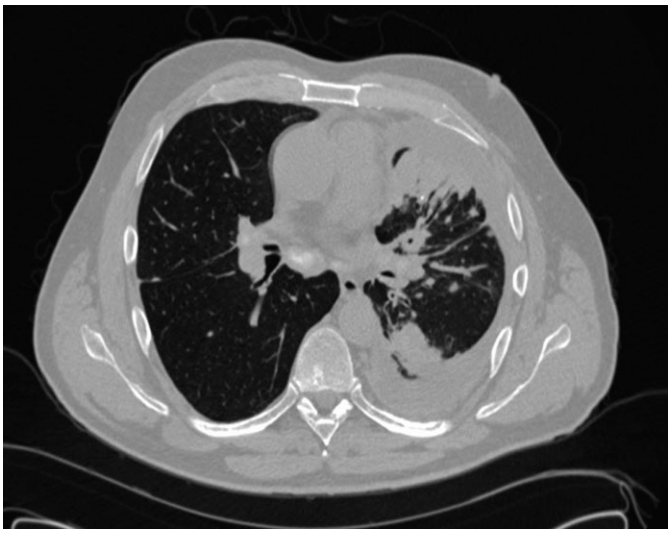

FIGURE 1. Computed tomography scan of the chest: lung window. Bronchovascular and subpleural nodules are shown. There is left-sided pleural effusion.

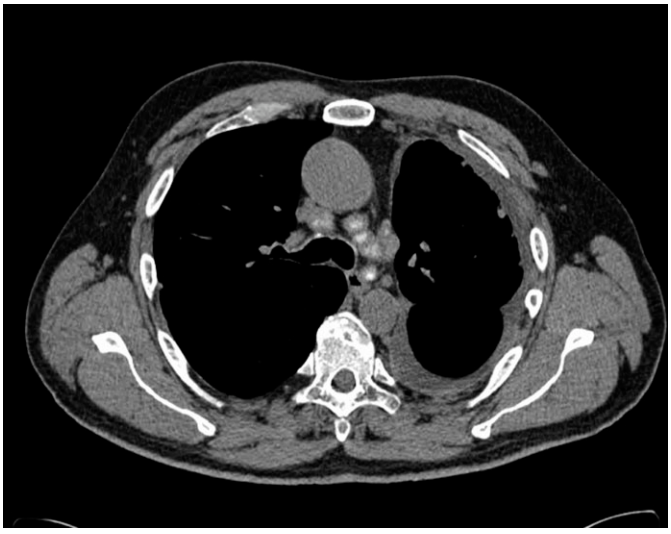

FIGURE 2. Computed tomography scan of the chest: mediastinal window. Bilateral hilar and mediastinal lymphadenopathies with faint central calcification are shown.

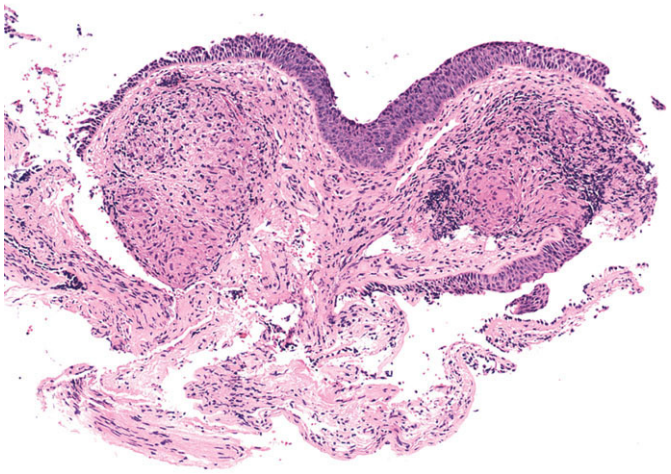

FIGURE 3. Transbronchial biopsy of the lung parenchyma: noncaseating granulomas.

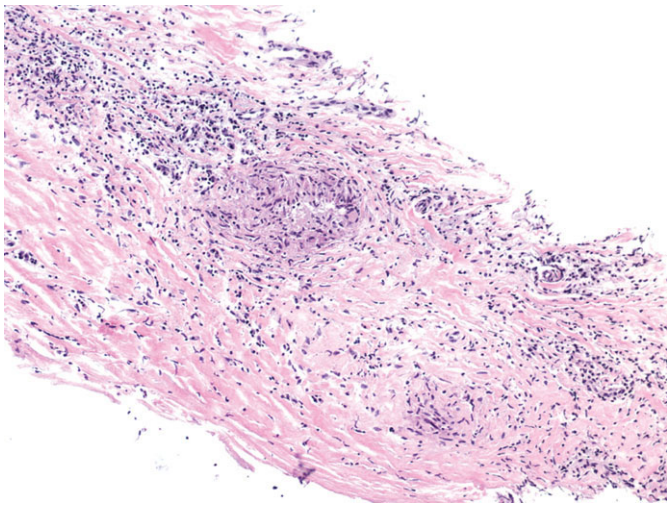

FIGURE 4. Pleural biopsy: noncaseating granuloma.

parenchymal disease, the prevalence of pleural effusions decreases, whereas pleural thickening and pneumothorax increase.[5] It is important to emphasize that 40% of pleural effusions in sarcoidosis may be due to other causes, such as tuberculosis and mesothelioma. Our patient was initially treated with itraconazole as histoplasmosis is most prevalent in the Central and Eastern United States, especially in Ohio River valleys, where this patient lived.

The prevalence of a pneumothorax in sarcoidosis is up to 4%.[1] Pleural thickening can be demonstrated in 11% to 71% of patients with pleural sarcoidosis, and 10% to 20% of these cases have thickening without effusion. Detection of subpleural nodules and cysts has been possible since the introduction of high-resolution CT scans. Their prevalence in sarcoidosis ranges from 22% to 76%, and they are often described as masses that correspond to nodules seen in both parietal and visceral surfaces. Hilar or mediastinal lymphadenopathy is present on CT in 47% to 94% of patients with sarcoidosis. Lymph node enlargement is usually bilateral, most commonly with right-sided predominance. The most involved stations are the right lower paratracheal, right hilar, subcarinal, aortopulmonary window, and right interlobar stations. Nodal calcification is noted in 53% with eggshell calcification present in 9%. The

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enlargement of internal mammary and pericardial lymph nodes requires the exclusion of lymphoma.[6]

The management of pleural sarcoidosis should be individualized because a majority of these effusions resolve spontaneously in 1 to 3 months.[5] There have been reports of resolution in 2 weeks with steroid therapy. Incomplete resolution of the pleural effusions with progression to chronic pleural thickening or a trapped lung has been reported. There is agreement that oral corticosteroid treatment should be considered in patients with severe persistent or progressively worsening respiratory symptoms or declining lung function. Severe symptoms can be considered as those that interfere with essential aspects of the patient's daily life.[7] The initial dosage of oral prednisone recommended by the American Thoracic Society, the European Respiratory Society, and the World Association of Sarcoidosis and Other Granulomatous Disorders guidelines is 20 to 40 mg/day.[8] Further evaluation is recommended after 1 to 3 months. If the patient responds, the dose should be reduced gradually to a maintenance dose, such as 5 to 15 mg/day of prednisolone. American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and Other Granulomatous Disorders guidelines advise treatment for at least 1 year. Immunosuppressive, cytotoxic, and immunomodulatory agents have been used to treat patients failing or experiencing adverse effects of steroids. Favorable responses have been reported with methotrexate, leflunomide, azathioprine, cyclophosphamide, chlorambucil, cyclosporine A, antimalarials, tumor necrosis factor α inhibitors, and thalidomide. Because of potential serious toxicities associated with cyclophosphamide and chlorambucil, these agents are not recommended.[9]

Our patient presented with pleural sarcoidosis with a pleural effusion and nodules. Treatment with 20 mg of prednisone daily was started initially. Four weeks after discharge, he was still dyspneic and had persistent left pleural effusion. He also had gained a significant amount of weight and developed bilateral lower extremity edema; these were thought to be secondary to prednisone treatment. Steroids were subsequently tapered, and leflunomide was started. His symptoms improved dramatically after 1 month of treatment with leflunomide and steroids, and 3 months later, his pleural effusion had completely resolved.

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