Sarcoidosis Pleural Effusion: A Not So Common Feature of a Well Known Pulmonary Disease

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Introduction

Pleural involvement in sarcoidosis with the development of pleural effusion is a not so common occurrence. The incidence reported in the literature is approximately 1–10%. Pleural effusion related to sarcoidosis is diagnosed when other more common etiologies are excluded. It is slightly more common on the right side, and is usually an exudate with lymphocytic predominance. I report a case of pleural effusion in sarcoidosis in which the CD4/CD8 T lymphocytes ratio and the level of angiotensin converting enzyme (ACE) were measured in the pleural fluid. Sarcoidosis pleural effusion should be considered in any patient with a pleural effusion and documented sarcoidosis, and it should be differentiated from other common causes of pleural effusions (eg, volume overload, malignancy, or infection).

Case Summary

In the out-patient office I saw a 55-year-old African-American woman with symptoms that had started 1 month before: dry cough, right-side pleuritic chest pain, and a 4.5-kg weight loss. She had had biopsy-proven sarcoidosis for the past 20 years. She had recently been to an emergency department, where she was prescribed antibiotics for presumed pneumonia, but she had no improvement. A computed tomogram showed a moderate-size right pleural effusion (Fig. 1), and thoracentesis obtained a clear yellow fluid that was found to be a lymphocytic (44%) exudate, with protein of 5.2 g/dL (serum 7.7 g/dL), lactate dehydrogenase of 121 U/L, no growth of bacteria, no malignant cells, a CD4/CD8 ratio of 2.61, and a pleural-fluid ACE of 19 U/L. A month later a follow-up computed tomogram showed a bigger persistent right effusion. At that point she was referred for thoracic surgery. She had a right-side video-assisted thoracoscopy, with lung and pleura biopsies. Intraoperatively, calcified nodules were noted in the pericardium and parietal pleura. The biopsy specimens showed non-caseating granulomas, without acid-fast bacilli (Fig. 2). She was started on low-dose daily prednisone and weekly methotrexate, which had been her regimen in previous exacerbations. Her symptoms completely resolved and the right effusion did not reappear. At 1-year follow-up she had had no recurrence of pleural sarcoidosis.

Discussion

Sarcoidosis is a systemic disease of unknown origin, that causes a typical granulomatous inflammation, in almost any organ.1 The lungs are commonly affected in various ways. The diagnosis of sarcoidosis relies on the histologic demonstration of non-caseating granulomatous inflammation. The incidence of sarcoidosis pleural effusion is probably 0.7–10% among patients with sarcoidosis, but one problem with that 0.7–10% value is that not every patient with sarcoidosis gets an exhaustive workup to look for pleural involvement. On the other hand, not every pleural effusion in patients with sarcoidosis is related to the sarcoidosis. In a recent consecutive series of patients with sarcoidosis who underwent chest ultrasonography, only 5 of 181 patients had a pleural effusion.2 Of those 5, just 2 were caused by biopsy-proven sarcoid pleural involvement.

The symptoms and signs of sarcoidosis pleural effusion range from completely asymptomatic to severe dyspnea and pleuritic pain in the affected area. In fact, some authors prefer to refer to it as sarcoidosis pleural disease, rather than just effusion, to emphasize that it could also represent pleural nodules, pleurisy, different types of effusion, or pneumothorax.3 These effusions are usually small to moderate size and more often right-sided than left-sided. With a sarcoidosis pleural effusion there is also usually

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some degree of pulmonary parenchymal abnormality, also related to the sarcoidosis.\(^4\)

The best imaging study for diagnosing sarcoidosis pleural effusion is computed tomogram,\(^5\) which allows detection at an early stage of pleural involvement (nodules, thickening) and of more advanced abnormalities (effusion, pneumothorax) and also gives information about lung parenchymal involvement. Chest ultrasound can also be useful in detecting even small effusions in patients with sarcoidosis,\(^6\) and for diagnostic and therapeutic interventions (eg, thoracentesis).

The fluid from a pleural effusion related to sarcoidosis is generally an exudate with lymphocytic predominance.\(^3\) Other types of fluid have been reported but are less common. As described by Huggins et al,\(^2\) in patients with sarcoidosis pleural effusion (as in our patient) there is a asynchrony between the protein and lactate dehydrogenase pleural/serum ratio, the first being much more elevated. In more complicated cases, pleural thickening may be associated with hemothorax or chylothorax or even trapped lung.

Regarding the lymphocyte subpopulation in the pleural fluid, there is usually an elevation of the CD4/CD8 ratio in patients with sarcoidosis pleural effusion. This was first described in 1984, by Groman et al.\(^7\) The CD4/CD8 ratio correlates with that usually found in bronchoalveolar lavage fluid in patients with active sarcoidosis, but is the opposite of the low ratio found in peripheral blood in these patients. The reason for that difference is unknown. The cardinal role of the CD4+ lymphocytes in the immunopathogenesis of sarcoidosis has been clearly defined.\(^8\)

There is scarce information in the literature about the ACE level in the fluid from a sarcoidosis pleural effusion.\(^9\) The ACE level in the pleural fluid has been reported, but there is no definition of the normal value. It is also unknown if ACE is elevated in patients with sarcoidosis exacerbation and pleural effusion.

Definitive diagnosis of sarcoidosis pleural effusion requires a pleural biopsy that shows granulomas and a negative acid-fast-bacilli stain. There is not enough information to state that all patients with a clinical picture compatible with sarcoidosis pleural effusion require a pleural biopsy, but probably in the majority of cases biopsy is necessary to rule out malignancy or infection that can mimic sarcoidosis pleural effusion, especially in areas where tuberculosis is endemic. In the past, most thorascopic biopsies were done by thoracic surgeons, but now, with the more widespread use of medical thoracoscopy, the interventional pulmonologist can obtain the biopsy.\(^10\)

In suspected sarcoidosis pleural effusion an open pleural biopsy is probably superior to a closed pleural biopsy because of the heterogeneous pleural involvement with granulomas. The treatment of sarcoidosis pleural effusion is not different from the current treatment of pulmonary sarcoidosis; a recent comprehensive review covered this topic well.\(^11\) There is no information about the impact of sarcoidosis pleural effusion in the overall prognosis of patients with sarcoidosis. Table 1 summarizes the most common characteristics of the sarcoidosis pleural effusion.

**Teaching Points**

A high index of suspicion is needed to make a diagnosis of sarcoidosis pleural effusion. In my patient I was able to exclude other common causes of pleural effusion, and I had the benefit of a video-assisted thoracoscopy and bi-
Sarcoidosis pleural effusion fluid is an exudate with lymphocytic predominance, with an elevated CD4/CD8 ratio, in contrast to the low CD4/CD8 ratio in peripheral blood in patients with sarcoidosis, and the low CD4/CD8 ratio in other conditions, such as amiodarone pleuropneumonitis. The ACE level in the sarcoidosis pleural effusion fluid has been reported, but the normal value is not known. It is also unknown if the ACE level is elevated in patients with exacerbation of sarcoidosis and pleural effusion. With more sensitive techniques to detect pleural effusions (ultrasound, computed tomography) it is expected that more patients with sarcoidosis will be diagnosed with effusions. The ideal is to analyze the pleural fluid so as to rule out other causes and identify sarcoidosis pleural effusion, maybe without requiring pleural biopsy. Further research is needed to determine if the pleural-fluid CD4/CD8 ratio and ACE level have a role in diagnosis.

REFERENCES


Table 1. Characteristics of Sarcoidosis Pleural Effusion

| Incidence of 0.7–10% in patients with sarcoidosis |
| Symptoms range from asymptomatic to dyspnea and pleuritic pain |
| Usually an exudate with lymphocytic predominance |
| CD4/CD8 ratio increased in many cases |
| Effusion size small to moderate |
| Right-sided more frequently than left-sided, but can be bilateral |
| Usually in the context of coexisting parenchymal lung involvement |
| More severe cases with chylothorax, hemothorax, pneumothorax |
| Definitive diagnosis via biopsy, which shows granulomas in the pleura |
| Good response to standard sarcoidosis treatment |