

## CLINICAL VIGNETTE

# Evaluation of Tuberculous Pleural Effusion

Joanne Bando, M.D., and Ravi Aysola, M.D.

### Case Presentation

A 21-year-old female with no significant past medical history presented with fevers, chills, dyspnea, productive cough, and vomiting for 1 week. She had never resided outside the United States and had no known tuberculosis exposures or HIV-risk factors. She had no personal or family history of malignancy and did not have any preceding weight loss or night sweats.

On physical examination, she was febrile to 102°F and diaphoretic. Respiratory rate was 20, and she was not using accessory muscles for respiration. Lung exam was notable for diminished breath sounds and dullness to percussion of the left chest. Initial labs revealed anemia with hemoglobin of 10 g/dL and a white blood count of  $7 \times 10^3$ . Chest X-ray showed opacification of the left hemithorax with mediastinal shift to the right (Figure 1).

Left thoracostomy tube was placed with output of approximately 2 liters of clear, serous fluid with fibrinous deposits. Fluid analysis revealed an exudative effusion (LDH 415 U/L, protein 5 g/dL) with lymphocytic predominance (segmented neutrophils 0%, lymphocytes 95%, monocytes 5%, mesothelial cells 0%). Gram stain and initial cultures were negative. Pleural fluid adenosine deaminase (ADA) was 11.9 U/L. The post-drainage chest computed tomography (CT) demonstrated left lower lobe consolidation, left hilar and interlobar lymphadenopathy, and nodular thickening of the parietal pleura. The pleural fluid cytology and flow cytometry were negative for malignancy.

Flexible videobronchoscopy was negative, including bronchoalveolar lavage. Three sputum smears were negative on AFB stain, and HIV and fungal studies, including coccidiomycosis IgG/IgM and histoplasmosis urine antigen, were negative. Serum MTB quantiferon GOLD assay was positive.

Pleural biopsy obtained via video assisted thoracoscopic surgery (VATS) demonstrated florid granulomas without evidence of malignancy. AFB smears and GMS stains for fungal elements were negative. The patient was diagnosed with primary pulmonary tuberculosis with tuberculous pleuritis and was started on empiric treatment with Rifampin, Isoniazid, Pyrazinamide, and Ethambutol (RIPE). Ten weeks later, respiratory cultures and pleural biopsy cultures grew *Mycobacterium tuberculosis*.

### Discussion

Tuberculous pleuritis can occur as a result of either primary *M. tuberculosis* infection or reactivation disease. This occurs in about 5% of patients with tuberculosis and typically presents with a febrile illness, cough, and pleuritic pain.<sup>1</sup>

Tubercular effusions are exudative, with protein level typically above 5 g/dL.<sup>2</sup> They may present as neutrophilic predominant effusions in the first few days but are lymphocytic predominant in up to 93% of cases.<sup>3</sup> Mesothelial cells are typically less than 5% of total cell count as they are prevented from entering the pleural space by lymphocytic infiltration of the pleura. Pleural fluid pH is  $< 7.4$ , and the glucose level is commonly comparable to serum glucose (60-100 mg/dL.) The effusion likely represents a delayed hypersensitivity reaction to tuberculous protein and carries a low bacillary burden, hence, pleural fluid AFB stains are rarely positive.<sup>4</sup> The ADA level may be useful (typically  $> 40$  U/L).<sup>3</sup> However, the ADA can also be elevated in other disease processes including malignancy and empyema in laboratories that do not distinguish the isoenzymes ADA-2 (increased in tuberculous effusions) from ADA-1.<sup>5</sup>

Diagnosis can be further assisted by pleural biopsy. Histopathologic examination of the pleural biopsy tissue has the highest diagnostic yield with demonstration of granulomas in 50-97% and positive cultures in 40-80%.<sup>3,6-9</sup> Sputum culture yield in HIV-negative patients is variable with positive *M. tuberculosis* cultures in 20-50% and with higher yield in patients with parenchymal findings. In one study, the yield of induced sputum for positive *M. tuberculosis* culture was 55%.<sup>1,6</sup> Pleural fluid AFB stains are low yield with 5.5% positive stains in a case series of 254 tuberculous effusions.<sup>3</sup> Pleural fluid cultures are positive for *M. tuberculosis* in less than 40%.<sup>8</sup> Culture data can take several weeks to become positive and thus other clinical indicators are typically needed to start timely antitubercular therapy.

This patient presented with a large unilateral pleural effusion without tuberculosis risk factors. The first appropriate step was pleural fluid analysis. This yielded an exudative, lymphocytic predominant fluid suspicious for tuberculous pleuritis or malignancy. Features of the pleural fluid consistent with tuberculous etiology were lymphocytic predominance (95%), elevated protein level (5 g/dL), and absence of mesothelial cells. The low pleural fluid ADA level was less consistent with tuberculous effusion. One possibility was this reported result was falsely low, as ADA can decrease linearly with degradation at ambient temperatures.<sup>10</sup> Pleural fluid

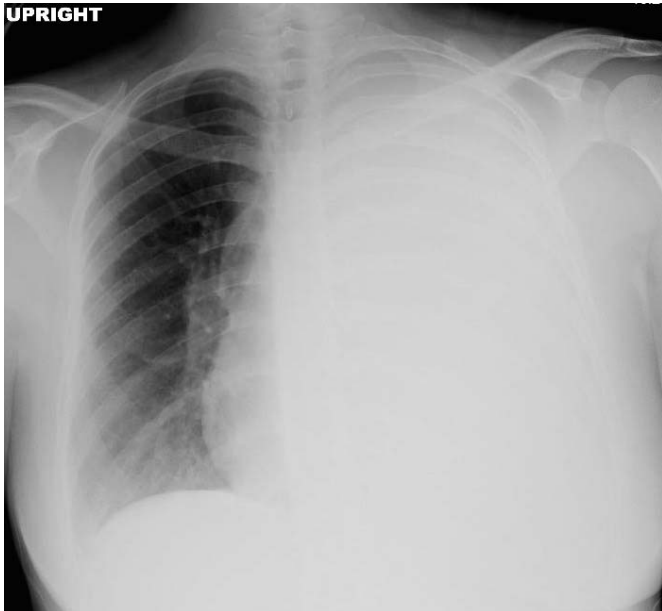
cytology and flow cytometry were negative for malignancy. Gram stain and fluid culture were nondiagnostic.

Further workup with chest CT post-fluid drainage demonstrated findings not definitive for malignancy or infection. The positive MTB Quantiferon GOLD assay added to the clinical suspicion but was not sufficient for diagnosis. The sputum AFB stains and preliminary cultures were negative and did not initially assist with diagnosis.

With the non-diagnostic workup and the remote possibility for malignancy, the decision was made to proceed with pleural biopsy. Combined with the positive MTB Quantiferon GOLD, the histopathology of granulomas provided sufficient clinical suspicion to initiate empiric antituberculous chemotherapy pending final cultures.

### Figures

**Figure 1.** Chest X-ray demonstrating opacification of the left hemothorax with contralateral mediastinal shift.



### REFERENCES

1. **Seibert AF, Haynes J Jr, Middleton R, Bass JB Jr.** Tuberculous pleural effusion. Twenty-year experience. *Chest.* 1991 Apr;99(4):883-6. PubMed PMID: 1901261.
2. **Light RW.** Update on tuberculous pleural effusion. *Respirology.* 2010 Apr;15(3):451-8. doi: 10.1111/j.1440-1843.2010.01723.x. Epub 2010 Mar 21. Review. PubMed PMID: 20345583.
3. **Valdés L, Alvarez D, San José E, Penela P, Valle JM, García-Pazos JM, Suárez J, Pose A.** Tuberculous pleurisy: a study of 254 patients. *Arch Intern Med.* 1998 Oct 12;158(18):2017-21. PubMed PMID: 9778201.
4. **Ellner JJ, Barnes PF, Wallis RS, Modlin RL.** The immunology of tuberculous pleurisy. *Semin Respir Infect.* 1988 Dec;3(4):335-42. Review. PubMed PMID:2463656.
5. **Gakis C.** Adenosine deaminase in pleural effusions. *Chest.* 1995 Jun;107(6):1772-3. PubMed PMID: 7781389.
6. **Conde MB, Loivos AC, Rezende VM, Soares SL, Mello FC, Reingold AL, Daley CL, Kritski AL.** Yield of sputum induction in the diagnosis of pleural tuberculosis. *Am J Respir Crit Care Med.* 2003 Mar 1;167(5):723-5. PubMed PMID: 12598215.
7. **Sahn SA.** State of the art. The pleura. *Am Rev Respir Dis.* 1988 Jul;138(1):184-234. Review. PubMed PMID: 3059866.
8. **Epstein DM, Kline LR, Albelda SM, Miller WT.** Tuberculous pleural effusions. *Chest.* 1987 Jan;91(1):106-9. PubMed PMID: 3792061.
9. **Gopi A, Madhavan SM, Sharma SK, Sahn SA.** Diagnosis and treatment of tuberculous pleural effusion in 2006. *Chest.* 2007 Mar;131(3):880-9. Review. PubMed PMID: 17356108.
10. **Bañales JL, Pineda PR, Fitzgerald JM, Rubio H, Selman M, Salazar-Lezama M.** Adenosine deaminase in the diagnosis of tuberculous pleural effusions. A report of 218 patients and review of the literature. *Chest.* 1991 Feb;99(2):355-7. PubMed PMID: 1824928.

Submitted June 2, 2015