

SECTION EDITOR: ENID GILBERT-BARNES, MD

Pathological Case of the Month

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A 16-YEAR-OLD GIRL was seen for fever, headache, malaise, and right-sided chest wall pain of 1 week's duration. Prior to presentation, she developed a dry cough and nighttime sweating. On admission, her temperature was 38.8°C; pulse, 100 bpm; respirations, 20 breaths per minute; blood pressure, 114/75 mm Hg; and oxygen saturation, 95% breathing room air. She had dullness to percussion and decreased breath sounds over the lower $\frac{2}{3}$ of the right posterior lung field. Upright and decubitus chest radiographs showed a free-flowing pleural effusion occupying $\frac{3}{4}$ of her right lung field. Further questioning revealed she had emigrated to the United States from Haiti 4 months earlier and had negative findings on purified protein derivative (PPD) testing 3 months earlier. Her white blood cell count was 6800/ μ L (64% neutrophils, 3% bands, 17% lymphocytes, and 16% monocytes). Values for hematocrit and platelet count were normal; serum total protein, 7.4 g/dL; serum lactate dehydrogenase (LDH), 578 U/L.

She underwent thoracoscopy and chest tube placement; 800 mL of serosanguinous fluid was drained. During thoracoscopy, 2- to 3-mm white lesions studding the pleura with occasional larger outgrowths were noted (**Figure 1**). A view toward the apex demonstrated similar lesions, and visceral pleura was adhered to parietal

pleura at the apex (**Figure 2**). Histopathologic findings of the pleural biopsy specimen showed chronic inflammation and caseating granulomas (**Figure 3**). Pleural fluid findings included pH 7.44; LDH, 743 U/L; glucose, 95 mg/dL (5.3 mmol/L); protein, 5.7 g/dL; red blood cell count, 9050/ μ L, and white blood cell count, 1740/ μ L (11% neutrophils, 81% lymphocytes, and 8% mononuclear histiocytes). Findings from gram stain of pleural fluid and Kinyoun stains of pleural fluid, pleural tissues, and sputum were negative for organisms. Routine bacterial culture of pleural fluid, pleural tissue, and blood; fungal culture of pleural fluid; and mycobacterial cultures of pleural fluid and pleural tissue were analyzed. A PPD test was placed.

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Figure 1.



Figure 2.

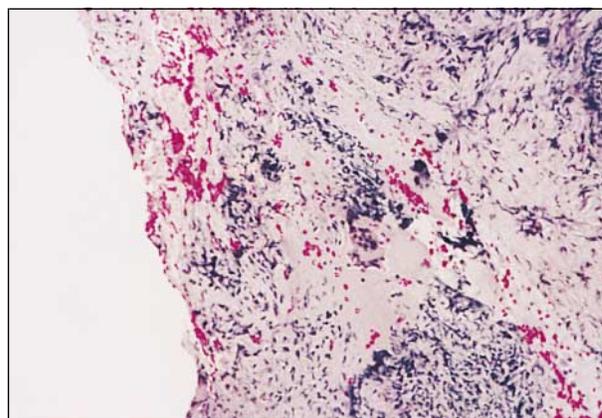


Figure 3.

Diagnosis and Discussion

Tuberculous Pleural Effusion

Figure 1. Thoracoscopic view of parietal pleura overlying right ribs. Note granulomas studding pleura, including 2 larger outgrowths seen in center (original magnification $\times 8$).

Figure 2. Thoracoscopic view of visceral pleura adhered to parietal pleura at lung apex. Collapsed right lung (secondary to selective left-lung ventilation during procedure) seen at base of photograph. Granulomas are noted diffusely over the parietal pleura. Granulomas on visceral pleura are not as prominent because that pleural surface is collapsed against right lung (original magnification $\times 8$).

Figure 3. Diffuse chronic inflammation and granulomas with multinucleated giant-cell formation in pleural tissue (hematoxylin-eosin, original magnification $\times 200$).

Pleural effusions can be divided into transudative and exudative processes. The fluid-serum ratio of protein is less than or equal to 0.5 for a transudate and greater than 0.5 for an exudate; the fluid-serum ratio for LDH is less than or equal to 0.6 for a transudate and greater than 0.6 for an exudate.¹ Other than tuberculosis (TB), possible infectious causes to exudative pleural effusions include pneumonias stemming from bacteria such as *Staphylococcus aureus*, group A streptococcus, *Haemophilus influenzae* type b, and *Mycoplasma pneumoniae*; viruses such as cytomegalovirus, herpes simplex virus, or influenza; or fungi such as *Blastomyces dermatitidis* and *Coccidioides immitis*. Noninfectious causes include malignancy, chylothorax, lymphangiectasia, uremia, infarction of either the heart or lung, collagen-vascular diseases, and drug reactions. Despite findings reported by earlier researchers, more recent large case series of tuberculous pleural effusion suggest that glucose in the pleural fluid can be variable.²

Definitive diagnosis of tuberculous pleural effusion requires analysis of multiple samples with mycobacterial stain and culture. The most sensitive culture material is the pleura itself, which demonstrates caseating granulomas in up to 90% of cases and positive culture findings in up to 70%, but only rarely shows acid-fast bacilli on stain. Acid-fast bacilli stain of pleural fluid is likewise usually negative, and pleural fluid cultures are only positive for *Mycobacterium tuberculosis* in 30% to 50% of cases.³ In our patient, only the pleural tissue culture became positive for *M tuberculosis* 35 days into incubation. Ancillary biochemical tests such as adenosine deaminase and interferon- γ levels in the pleural fluid can be used as adjuncts in diagnosis.² For patients with a clinical presentation compatible with tuberculous pleural effusion, positive PPD findings, and pleural biopsy results showing granulomatous inflammation, TB is virtually certain, and therapy is usually begun with 3 to 4 antituberculous medications.² Our patient received isoniazid, rifampin, pyrazinamide, and ethambutol before the culture results were available.

Tuberculous pleural effusion can be a manifestation of either primary or reactivation disease.² This patient had negative PPD results on arrival to the United

States, but her PPD was positive at 22 mm within 48 hours of this admission. One would suspect that TB manifesting 4 months after emigration resulted from primary infection in the country of origin. Tuberculous pleural effusion is thought to represent a delayed hypersensitivity response to mycobacterial antigens in the pleural space, which gain access via rupture of subpleural caseous foci.⁴ The low organism burden nevertheless gives rise to the presence of an immunologically mediated effusion that causes most symptoms seen in these patients.² Left untreated, tuberculous pleural effusion usually resolves spontaneously but later returns as active TB. In a series of 141 military personnel with serofibrinous pleural effusions and positive PPD findings, 92 (65%) subsequently developed some form of active TB, although most had originally resorbed their effusions in the absence of chemotherapy.⁵ Risk factors for progression to active TB include recently acquired disease, immunocompromised status, increased exposure inoculum, and certain age groups (≤ 5 years, ≥ 60 years, or postpubertal adolescence).³ The overall incidence of TB is decreasing in the United States, but the proportion of cases among foreign-born children continues to rise. Haitian immigrants have rates of TB greater than 50 per 100 000 person years (>6 times the rate for the US population) in the first 5 years after arrival.⁶ Annually, about 1000 cases of pleural TB are reported in the United States. Although only 15% of patients with TB have extrapulmonary disease, roughly 1 in 30 have tuberculous pleural effusion.⁷

Accepted for publication April 18, 2000.

We thank Steven Moulton, MD, and Dongfen Chen, MD, for providing the photographs for the case, and to Jerome Klein, MD, for his editorial assistance.

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REFERENCES

1. Light RW, MacGregor I, Luchsinger PC, Ball WC. Pleural effusions: the diagnostic separation of transudates and exudates. *Ann Intern Med.* 1972;77:507-513.
2. Light RW. Tuberculous pleural effusions. In: Light RW. *Pleural Diseases*. 3rd ed. Baltimore, Md: Williams & Wilkins; 1995:154-166.
3. Jacobs RF, Starke JR. Mycobacterium tuberculosis. In: Long SS, Pickering LK, Prober CG, eds. *Principles and Practice of Pediatric Infectious Diseases*. New York, NY: Churchill Livingstone Inc; 1997:881-904.
4. Stead WW, Eichenholz A, Staus H-K. Operative and pathologic findings in twenty-four patients with syndrome of idiopathic pleurisy with effusion, presumably tuberculous. *Am Rev Tuberc Pulm Dis.* 1955;71:473-502.
5. Roper WH, Waring JJ. Primary serofibrinous pleural effusion in military personnel. *Am Rev Tuberc Pulm Dis.* 1955;71:616-634.
6. Zuber PL, McKenna MT, Binkin NJ, Onorato IM, Castro KG. Long-term risk of tuberculosis among foreign-born persons in the United States. *JAMA.* 1997;278:304-307.
7. Mehta JB, Dutt A, Harvill L, Mathews KM. Epidemiology of extrapulmonary tuberculosis. *Chest.* 1991;99:1134-1138.