Pleural Effusion and Fever in an Immunocompromised Patient

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CASE REPORT

A 15-year-old female with a past medical history significant for autoimmune hepatitis on chronic immunosuppressive medications presented to a community hospital with a 24-hour history of shortness of breath, right-sided pleuritic pain, cough, fever, and headache. Review of systems was otherwise negative. She was diagnosed with pneumonia and admitted for empiric treatment with ceftriaxone, clindamycin, azithromycin, and fluconazole. She remained febrile and was transferred after 72 hours to a quaternary children’s hospital. Her past medical history was significant for autoimmune hepatitis diagnosed in 2005, and home medications included 6-mercaptopurine and allopurinol. The patient was born and lives in coastal central California. She traveled 1 month before presentation to Arizona and 1 year prior to visit family in Mexico, both trips were 2 weeks in duration. She had no known sick contacts.

Her physical exam upon transfer was notable for a generally well appearance. Her vital signs were as follows: blood pressure 102/67; heart rate 80; respiratory rate 21; SpO2 97% on room air; and temperature 38.1°C. She had decreased breath sounds and dullness to percussion on the right. There was no cervical, axillary, or inguinal lymphadenopathy. Her abdominal exam was benign. The patient was continued empirically on ceftriaxone, clindamycin, azithromycin, and fluconazole. She remained febrile and was transferred after 72 hours to a quaternary children’s hospital. Her past medical history was significant for autoimmune hepatitis diagnosed in 2005, and home medications included 6-mercaptopurine and allopurinol. The patient was born and lives in coastal central California. She traveled 1 month before presentation to Arizona and 1 year prior to visit family in Mexico, both trips were 2 weeks in duration. She had no known sick contacts.

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On day 5 of illness, a chest tube was placed draining 750 mL of exudative serous fluid with 1240/μL nucleated cells and 92% lymphocytes. The adenosine deaminase was 5.1 U/L (0–9.4). Acid-fast bacilli (AFB), fungal, and bacterial stains were negative as were a mycobacterial and mycoplasma polymerase chain reaction (PCR). Cytology was negative for malignant cells. Her fevers resolved the day after chest tube placement. A pleural biopsy was performed on day 8 of her illness, and fibrinous material was noted in the pleural space intraoperatively. Acid-fast bacilli, fungal, and bacterial stains were negative as was bacterial sequencing, which can identify Mycobacterium tuberculosis complex. Pathology revealed necrotizing granulomatous inflammation but no well formed granulomas. Three induced sputa were AFB smear negative. She remained afebrile and was discharged with presumed latent tuberculosis infection but without a clear diagnosis for her disease after completing a 10-day course of ceftriaxone and 5 days of azithromycin. Fluconazole was also discontinued. On follow-up 1 month after discharge she remained afebrile; however, she had shortness of breath with exertion. Her pleural effusion was unchanged on chest radiograph from the time of discharge. Her M pneumoniae serologies were IgM 1:256 and IgG 1:256 and Histoplasma serologies...
were negative. All AFB cultures from sputum, pleural fluid, and pleural biopsy remained negative.

**DISCUSSION**

**Diagnosis: Pleural Tuberculosis due to Mycobacterium bovis**

The patient’s pleural biopsy culture became positive for *M. bovis* after 35 days. All other cultures were finalized negative. She was then treated with isoniazid, rifampicin, and ethambutol for 2 months followed by 7 months of isoniazid and rifampicin, with resolution of her shortness of breath and pleural effusion. Her exposure history revealed ingestion of cheese brought from Mexico by her grandfather 6 months before presentation, which placed her at risk for *M. bovis* infection.

We present a case of a moderately immunosuppressed adolescent who ultimately was diagnosed with pleural tuberculosis secondary to *M. bovis*. The patient presented acutely with only a 1-day history of fever and chest pain possibly consistent with community-acquired pneumonia and parapneumonic effusion. However, she had minimal airspace disease and was well appearing given the size of the effusion. Her well appearance, exposures, lymphocytic pleural fluid, and necrotizing granulomatous inflammation pointed toward a more indolent infection such as coccidioidomycosis, histoplasmosis, or mycobacterial disease. Noninfectious etiologies such as lymphoma were also considered and excluded.

The patient was not treated empirically for culture-negative tuberculosis disease because of her high risk for medication-related complications, her resolution of fever, and negative preliminary testing. This decision must be made on a case-by-case basis. Her exposure to unpasteurized dairy products was concerning, but *M. bovis* after ingestion typically presents with intra-abdominal disease or cervical lymphadenopathy. In the absence of a source case, a microbiologic diagnosis should be aggressively pursued if there is concern for mycobacterial disease. Treatment for latent tuberculosis infection should not be initiated until disease has been definitively excluded or an alternate diagnosis has been established. In this case, both the patient’s tuberculin skin test and QuantiFERON-Gold IT assay were positive. The QuantiFERON-Gold IT detects infection by *M. tuberculosis* complex organisms, *M. tuberculosis, M. bovis*, and *Mycobacterium africanum*, but not *M. bovis*-derived Bacillus Calmette–Guérin (BCG) strains.

Pleurisy secondary to *M. tuberculosis*, or in this case *M. bovis*, can be a challenging diagnosis. Cultures and PCR-based testing of pleural fluid is rarely helpful in making the diagnosis, and sputum cultures are positive in only 50% of cases. The pleural effusion represents an immune response to mycobacterium in the pleural tissue, resulting in the low diagnostic yield. Pleural fluid adenosine deaminase has a reported sensitivity of >90% [1], but it was negative in this case. Pleural biopsies is the critical test in the diagnosis of pleural tuberculosis. In contrast to pleural fluid culture, the sensitivity of a pleural biopsy culture is greater than 90%. Granulomata on pathology are consistent with tuberculosis; however, granulomatous inflammation is a more nonspecific finding indicative of chronic inflammation. The sensitivity of PCR testing of pleural tissue remains undefined, although from sputa the sensitivity in our laboratory is greater than 90% in smear-positive cases, which this patient’s was not.

In this patient’s case, the identification of *M. bovis* occurred within 24 hours of growth in liquid media and confirmatory *M. tuberculosis* complex PCR. This rapid diagnosis, with its rapidly growing bacilli, allowed effective treatment initiated soon after the patient’s discharge from the hospital. Pleural tuberculosis should be included in the differential diagnosis of pleural effusions in immunocompromised hosts as well as in the immunocompetent host. The presence of granulomas or necrosis on histology should lead to consideration for tuberculosis. The use of PCR to detect mycobacterial DNA is a sensitive diagnostic test that can be utilized in these situations.

**Figure 1.** (A) Posterior-anterior chest radiograph of a large, free-flowing, right-sided pleural effusion. (B) Large, right-sided pleural effusion with compression atelectasis and no intrathoracic lymphadenopathy or parenchymal disease.
identification was possible using a PCR assay designed to identify regions of difference- and species-based genomic deletions within the *M. tuberculosis* complex [2]. However, this assay is not available in most clinical laboratories, and the identification of *M. bovis* is often made presumptively based on the isolates’ drug sensitivities before laboratory send-out results return. *Mycobacterium bovis* is intrinsically resistant to pyrazinamide; however, monoresistance to pyrazinamide does not exclude *M. tuberculosis* or *M. bovis*-derived BCG, when clinically relevant, and therefore identification to the species level should be obtained [3].

*Mycobacterium bovis* is part of the *M. tuberculosis* complex and currently causes 1%–2% of reported tuberculosis cases in the United States. The low rate in the United States and other industrialized nations is attributed to screening and culling of cattle infected with *M. bovis* in addition to pasteurization; however, this practice is rare in developing countries, and bovine tuberculosis is considered enzootic throughout much of the world [4]. Polymerase chain reaction analysis of culture-positive tuberculosis isolates from Mexico identified *M. bovis* in 28% of the human samples in a location where as many as 16% of cattle are thought to be infected with *M. bovis* [5]. A report from San Diego, where there is a large bi-National Hispanic population, identified *M. bovis* in 6% of culture-positive adult cases and 35% of culture-positive pediatric cases [6]. *Mycobacterium bovis* is also the etiology for an increased proportion of tuberculosis cases in urban Hispanic communities far removed from the Mexican border [7].

The primary mechanism for infection in the United States is ingestion of imported unpasteurized dairy products. Although *M. bovis* can cause pulmonary tuberculosis, extrapulmonary disease, scrofula, and intra-abdominal disease in particular are more common in US cases (51% and 19%, respectively, of cases in the San Diego series) [6]. Intra-abdominal disease may manifest as gastrointestinal enteritis or colitis, peritonitis with peritoneal nodules, or intra-abdominal lymphadenopathy. Pulmonary disease is rare in children in the United States who are typically exposed via ingestion. However, among *M. bovis* cases originating in people born in endemic countries, 44% present with pulmonary disease, which suggests that aerosolized exposure is more common either through exposure to infected cattle or person-to-person spread [8].

Person-to-person spread is well documented in individuals infected with HIV; however, it has been described in immunocompetent patients as well and manifests more typically as pulmonary disease [9]. As with *M. tuberculosis*, nosocomial transmission and rapid progression from infection to disease has been documented in HIV-infected patients infected with *M. bovis* [10]. It is generally thought that patients who carry an increased risk for disease due to *M. tuberculosis*—because of immunosuppression for solid organ transplantation, stem cell transplantation, or autoimmunity—also have an increased risk for disease due to *M. bovis*. However, perhaps due to the relative rarity of disease due to *M. bovis* in resource-rich countries, there are only case reports describing *M. bovis* disease in solid organ transplant and stem cell transplant recipients [11,12].

In populations where *M. bovis* is common, there are clinical implications when treating culture-negative tuberculosis. *Mycobacterium bovis* is intrinsically resistant to pyrazinamide, and therefore a 9-month treatment course is recommended. This difference in treatment underlines the importance of obtaining a diagnosis by culture or PCR. In patients with possible tuberculosis disease and potential exposure, *M. bovis* should be considered in the differential diagnosis because of differences in treatment.

In summary, it is important to assess for zoonotic risk factors in patients presenting with clinical disease concerning for tuberculosis but without an identified tuberculosis contact. Patients, especially those who are immunocompromised, should be counseled to avoid unpasteurized dairy products, particularly from countries where bovine tuberculosis is endemic. Lastly, identification of *M. tuberculosis* complex isolates to the species level should be attempted if possible because the presence of *M. bovis* can have treatment and epidemiologic significance.

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**References**


