TUBERCULOSIS PLEURAL EFFUSIONS AND A CASE OF EMPYEMA NECESSITATIS (NECESSITANS)

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CASE HISTORY

A 15 year old pregnant female presented to the emergency department of a local hospital with respiratory distress at 32 weeks gestation. She had failed to gain weight appropriately during her pregnancy and throughout her third trimester of pregnancy had cough, shortness of breath and night sweats. She had an abnormal chest radiograph suggesting miliary tuberculosis and bilateral pleural effusions left side greater than the right. The patient was sent by air ambulance to a tertiary referral center where she was treated with broad spectrum antibiotic therapy in addition to multi-drug antituberculosis therapy including coverage for possible drug resistant TB with isoniazid, rifampin pyrazinamide, ethambutol, moxifloxacin and amikacin. Due to respiratory distress, labor was induced and a healthy baby was delivered vaginally. Initial evaluation of the child showed no evidence of tuberculosis.

The patient was noted on admission to have an anterior chest wall abscess. Thick, purulent fluid was obtained which was very difficult to aspirate. The abscess fluid was AFB smear positive and subsequently grew M TB sensitive to all first line antituberculous medications. Ultrasound and CT examination following delivery suggested that the pleural fluid was too thick to be aspirated or evacuated. Following delivery, the patient was able to produce sputum that was smear and subsequently culture positive for M TB. The patient responded well to the antituberculosis therapy in general, including, resolution of fever, decrease in cough, normalization of albumin and improvement in the bilateral pulmonary densities and effusions. The chest mass decreased in size following the initial aspiration and then enlarged to a 2 X 2 cm tender area of fluctuance without erythema in her right lower anterior chest. A CT scan of the chest revealed bilateral pleural effusions with extension of the pleural fluid on the right between her ribs into the soft tissues of her anterior chest wall (empyema necessitatis). After approximately 4 weeks of antituberculosis therapy she underwent a right video assisted thoracoscopy (VATS) with complete decortication of the anterior chest wall and pleural abscess. The surgeon noted a clear tract through the chest wall into the right pleural space. The patient had an uneventful postoperative recovery with no drainage from the surgical incision.

CASE DISCUSSION

PATHOPHYSIOLOGY

*Mycobacterium tuberculosis* affects the pleura at different stages of pulmonary and systemic disease as the pleura can be involved in either primary or post-primary (reactivation) TB disease. In primary disease, pleural TB occurs as a result of mycobacterial antigen entering the pleural space, perhaps due to the rupture of a subpleural caseous focus, causing a delayed hypersensitivity (DTH) immunogenic reaction mediated primarily by CD4 cells but also involving other inflammatory cells and a complex array of inflammatory mediators including interferon gamma and tumor necrosis factor alpha. The initial cellular reaction in the first 2-5 days is macrophage predominate but from then onward, lymphocytic cells generally predominate and PPD reactivity is usually found. Paradoxically, PPD reactivity may be delayed in some patients, possibly as a consequence of the sequestration of DTH mediating cells, such as CD4 cells, in the pleural space. This form of TB pleural effusion is pauci-bacillary and tubercle bacilli are typically difficult to isolate in this setting. In contrast, tuberculous empyema is a chronic active infection of the pleural space that contains a large number of tubercle bacilli, also likely introduced into the pleural space via rupture of a subpleural caseous focus. Other factors predisposing to this type of effusion may be progression of a primary TB pleural effusion or direct extension of infection into the pleural space from a tubercle on the surface of the lung or from thoracic lymph nodes. Hematogenous spread of the organism to the pleural space is also possible, especially in immune compromised patients. The accumulation of fluid is multi-factorial, but the primary mechanism is likely intense inflammation that impedes lymphatic drainage of the pleural space.

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EPIDEMIOLOGY
The frequency of tuberculous pleural effusions varies by location. In the United States they are relatively rare, occurring in perhaps 3-5% of all tuberculosis cases, and are reportedly the 10th most common cause of pleural effusion in the U.S. (see below). In contrast, in areas of the developing world where TB is more endemic than in the U.S., TB is the most common cause of pleural effusion, especially exudative pleural effusion. In the industrialized world, pleural effusion with TB is more likely due to reactivation of TB disease whereas in the developing world it is more likely a manifestation of progressive primary disease. In that context, HIV coinfection and multidrug resistant TB are altering the epidemiology of TB pleuritis. In one series, the incidence of TB pleural effusions in HIV/TB coinfected patients was as high as 90%.

CLINICAL PRESENTATION
For some patients with TB pleural effusions associated with primary tuberculosis, the appearance of pleural fluid may occur without symptoms and the pleural effusion is recognized only when a chest radiograph is done as part of a routine evaluation. This combination of minimal symptomatology and lack of sensitive culture techniques (see below) would suggest that tuberculous effusions, especially those associated with primary disease are under-diagnosed. More commonly, however, the illness is manifested by onset of fever, cough, pleuritic chest pain and dyspnea. 90% of patients have symptoms for less than one month. TB pleural effusions affect one hemithorax in 90-95% of cases. Massive effusions are unusual. Untreated pleural effusion as a manifestation of primary TB is usually a self-limited inflammatory process. In 90% of cases, there is complete resolution, even without treatment, spontaneously occurring within weeks to months. However, even this relatively benign and self-limited process is an important harbinger of the progression to active pleuro-pulmonary or extrapulmonary disease which occurs in 40-60% of patients with untreated pleural effusions within 5 years. Residual pleural thickening is also common and may occur in 50% of cases. Patients with TB empyema are invariably symptomatic with fever, sweats, cough, dyspnea and pleuritic chest pain. This type of effusion will not spontaneously resolve and may progress to more serious complications such as empyema necessitatis.

DIAGNOSIS
Tuberculin skin testing or interferon gamma release assay (IGRA). A positive PPD or IGRA, alone, is not adequate for diagnosing TB pleural effusion but can be important supportive evidence in the appropriate context. Conversely, a negative PPD or IGRA does not rule out the diagnosis. As noted previously, sequestration of DTH cells in the pleural space may delay the onset of the positive PPD, but the majority of patients with TB pleural effusion (excluding patients with advanced immune suppression) will at some point in the course of the illness have a positive PPD or IGRA.

Thoracentesis to obtain pleural fluid for cellular, biochemical and microbiological analysis is an absolutely essential element for diagnosing tuberculous pleural effusions. There is no substitute for obtaining pleural fluid for analysis. TB effusions are exudative, sometimes with protein concentrations > 5 g/dL. The differential cell count is almost invariably lymphocyte predominant (>50% lymphocytes), although for some effusions, especially TB empyema, in the first few weeks there may be a polymorphonuclear (PMN) cellular predominance that evolves into the classic lymphocyte predominant effusion. Cellular findings in the fluid that do not suggest TB effusion include a differential cell count with > 5% mesothelial cells or > 10% eosinophils (unless there is concomitant pneumothorax or intrapleural bleeding which can be associated with a high pleural fluid eosinophil count).

Pleural fluid should be sent for AFB staining and culture, even though microbiological analysis is not a sensitive diagnostic tool. However, positive cultures remain the gold standard for diagnosis. AFB smears are positive in only approximately 20-25% of TB effusions, although that percentage would be higher with TB empyema or in HIV coinfected patients. Cultures are positive in a many as 40% of TB

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effusions, again higher with TB empyema and HIV coinfection. These figures vary with populations studied and the type of TB effusion present, but they demonstrate the importance of ancillary testing for confirming the diagnosis of TB effusion in a majority of patients.

Some patients, perhaps 20%, will also have evidence of parenchymal lung involvement associated with TB effusion. The parenchymal involvement is usually on the same side of the chest as the effusion. This percentage would likely be higher with the use of chest CT scanning. The yield from sputum analysis is sometimes confirmatory with sputum smears positive in approximately 20% of patients. Sputum AFB cultures may be positive in as many as 50% of patients with aggressive efforts to collect sputum, such as sputum induction. As with pleural fluid specimens, the yield of sputum AFB analysis varies with the population studied and the type of TB effusion.

Adenosine deaminase (ADA) is the enzyme that catalyzes the conversion of adenosine to inosine and is found in high concentrations in TB pleural effusions. Values of ADA > 70 U/L are virtually diagnostic of TB effusions and values < 40 U/L virtually exclude the diagnosis of TB effusion. The higher the ADA value, the more likely TB is the diagnosis. The differential diagnosis of elevated ADA in a pleural effusion includes empyema (bacterial) and rheumatoid pleuritis which can usually be eliminated as possibilities after taking into account the other factors included in the pleural fluid analysis such as cell type predominance in the pleural fluid. Overall, an ADA level > 40 U should raise suspicion of TB pleural effusion. In one recent meta analysis the sensitivity and specificity of ADA for diagnosing TB effusions were 92% respectively. ADA levels are widely available and relatively inexpensive. This test is almost universally recommended for suspected TB pleural effusions, but clinically underutilized. Some authors propose measurement of interferon gamma (IFG) in pleural effusions to differentiate TB effusions from other etiologies. An IFG cutoff of 3.7 IU/ml in one study had a sensitivity of 98% and specificity of 98% for diagnosing TB effusions. This test is not yet widely available or approved for use in this setting.

Closed pleural biopsies, while potentially quite helpful when performed by experienced clinicians is a procedure that is done with progressively less frequency due to declining numbers of clinicians who are comfortable and experienced with this procedure. Currently, pleural biopsies are more likely done via video assisted thoracoscopy (VATS) either by a pulmonary physician or thoracic surgeon. Pleural biopsies have the advantage of demonstrating pathologic changes such as granulomatous inflammation in the parietal pleura with AFB smears positive in 26% and cultures positive in 56% in patient with TB effusions. The differential diagnosis of granulomatous pleuritis includes fungal disease, sarcoidosis, and rheumatoid disease. Pleural biopsies are generally reserved for patients who prove to be diagnostic delimas after other less invasive evaluation is inconclusive. Additionally, biopsies may be necessary for patients in whom malignancy is a concern as malignant pleural effusions also present as a lymphocyte predominant exudates.

The nucleic acid amplification tests (NAAT) offer extremely high diagnostic specificity (> 95%) but variable diagnostic sensitivity for non-respiratory specimens such as pleural fluid. Currently, neither of the commercially available NAAT are FDA approved for use in the diagnosis of extra-pulmonary TB. At some point, these test may prove to be a very valuable addition to the diagnostic evaluation of pleural TB.

DIAGNOSIS SUMMARY

The diagnosis of TB pleural effusion includes clinical suspicion, radiographic confirmation of pleural fluid, +/- radiographic evidence of parenchymal tuberculosis disease, thoracentesis with protein/LDH measurement, cell count and differential, ADA level, AFB smear and culture. Sputum AFB smear and culture (induced if necessary). Pleural biopsy would then be considered under some circumstances.
TREATMENT

TB effusions associated with primary TB usually resolve spontaneously. For large effusions that cause respiratory compromise, an attempt to externally drain the effusion by thoracentesis or by pigtail catheter would be indicated. Indwelling tube thoracostomy is rarely necessary in this circumstance. Appropriate antituberculosis therapy should also be instituted. The role of steroids is controversial in this context with the exception of effusions associated with immune reconstitution syndrome in which case, steroids may be of substantial benefit, as with other manifestations of the IRIS syndrome.

TB empyemas should also be approached initially in a conservative fashion with institution of adequate multidrug antituberculosis therapy and an attempt to drain the effusion by thoracentesis or pigtail catheter. These effusions a) tend to recur and b) tend to septate and loculate, so it may be difficult to completely remove the fluid by external drainage. Sometimes serial thoracenteses are necessary to minimize fluid reaccumulation. Even complete removal of pleural fluid, however, may not decrease the amount of residual pleural thickening. Tube thoracostomy should only be considered under specific circumstances such as bronchopleural fistula, which is likely not to heal spontaneously. Chest tubes tend to be associated with prolonged fluid drainage and may also be associated with pleural-cutaneous fistulas when removed. Pleural decortication is generally not considered until the patient has had at least 6 months of therapy and then only if there is significant residual pleural fibrosis with pulmonary function restriction. The majority of TB empyemas will improve sufficiently (minimal residual pleural thickening/fibrosis) with medication alone so that surgical intervention is not necessary. Surgery may be necessary with a thick residual pleural rind and significant lung restriction or in the rare case of empyema necessitatis.

EMYPEMA NECESSITATIS

Empyema Necessitatis is a rare complication of tuberculous empyema whereby the infected pleural fluid penetrates through the pleural space and chest cavity into the chest wall and then, without intervention, may spontaneously drain through the skin of the chest wall, creating a pleural-cutaneous fistula (and sometimes a bronch-pleuro-cutaneous fistula). Extension of the purulent fluid occurs along the path of least resistance and along tissue planes. Increased pressure within the pleural loculation, chonic inflammation, and necrosis with erosion and fluid extension all contribute to this process. TB is reported to be the most common cause of empyema necessititates in the U.S. followed by actinomycosis. Prior to the advent of effective antituberculosis drugs, empyema necessitatis was associated with a high mortality. In the current era of effective anti-tuberculosis medication, the occurrence and mortality of this process have dramatically declined. In fact, it has become so unusual, that few current TB clinicians have experience with empyema necessitatis and few reference texts or review manuscripts offer specific instruction or advice on handling this potentially dangerous and disfiguring TB complication. The consensus appears to be that aggressive measures are necessary including appropriate aggressive antituberculosis therapy, early surgical intervention, preferably by VATS, with elimination of the abscess penetrating the chest wall and decortication of the adjacent infected pleural space. Early recognition is the key to successful therapy. Consultation with clinicians, including thoracic surgeons, experienced with empyema necessitatis is strongly advised.
TEACHING POINTS and KEY CONCEPTS

1. Pleural effusions are a relatively uncommon complication of tuberculosis but can occur with primary tuberculosis, reactivation tuberculosis and as part of an immune reconstitution response.

2. Pleural effusions associated with primary tuberculosis are due to a delayed type hypersensitivity response to tuberculosis antigens in the pleural space. These effusions are generally self limited and resolve spontaneously.

3. Tuberculous empyemas are due to persistence of \( M. \) \textit{tuberculosis} organisms in the pleural space that results in a purulent effusion that will not resolve spontaneously.

4. The evaluation of pleural effusions in patients with suspected or diagnosed tuberculosis requires a thoracentesis. Most primary care clinicians should be able to perform this procedure. Ultrasound guidance is a useful adjunct for safely guiding the placement of the thoracentesis needle/catheter.

5. Pleural fluid from the thoracentesis should be sent for
   a. LDH and protein concentrations
   b. Cell count and differential
   c. AFB smear and culture
   d. Adenosine deaminase (ADA) level

6. The characteristic profile of a tuberculous pleural effusion is an exudate with a lymphocyte predominance associated with an ADA level > 40 U/L. AFB cultures are positive in less than 50% of tuberculous effusions, but are highly specific when positive.

7. Patients with pleural effusion or empyema who are suspected to have active TB should have smears and cultures of sputum in addition to those done on the pleural fluid. Nucleic acid amplification (NAA) should be considered if sputum is AFB smear negative as up to 80% of smear negative active TB will be positive by NAA. Sputum smears are negative in 50% of persons with active pulmonary TB. Even in the absence of obvious pulmonary densities, sputum cultures will be positive 40-50% of patients with TB involving the pleural space. Induced sputum should be attempted if the patient is not able to spontaneously provide natural sputum. Having the patient try to obtain a specimen upon arising after a warm shower may also be helpful if sputum induction is not available.

8. In general, effusions associated with primary TB require intervention only if there is respiratory compromise. TB empyemas should be drained by thoracentesis or pigtail catheter if possible. Repeated procedures may be necessary for recurrent effusions. Tube thoracostomy should be reserved for special circumstances such as TB empyema associated with bronchopleural fistula.

9. Surgical intervention (pleural decortication) for patients with TB empyemas is usually reserved for patients who have been treated with adequate antituberculosis therapy at least 6 months and have large residual pleural fluid/fibrosis with significant lung restriction.

10. Treatment of empyema necessitatis involves both adequate antituberculosis therapy and surgical drainage of the chest wall abscess as well as the pleural space abscess with local pleural decortication.

11. For questions about management of TB pleural effusions, expert consultation should be requested.
(Above Left) 15 year old female with pleuropulmonary tuberculosis. Bilateral primarily nodular densities in the lung parenchyma with loss of the right costophrenic angle due to a pleural effusion.

(Above Right) Chest radiograph of the same 15 year old female after thoracoscopic drainage of the chest wall abscess and tuberculous empyema in the right pleural space with pleural decortication in the lower right pleural space.

(Left) Chest CT cut from the same 15 year old female demonstrating extension of the pleural fluid into the chest wall causing a bulge in the skin over the abscess created in the chest wall.

REFERENCES


