When a patient presents with new pleural effusion, the diagnosis of tuberculous (TB) pleuritis should be considered. The patient is at risk for developing pulmonary or extrapulmonary TB if the diagnosis is not made. Between 3% and 25% of patients with TB will have TB pleuritis. The incidence of TB pleuritis is higher in patients who are human immunodeficiency virus (HIV)-positive. Pleural fluid is an exudate that usually has a predominance of lymphocytes. The easiest way to diagnose TB pleuritis in a patient with lymphocytic pleural effusion is to demonstrate a pleural fluid adenosine deaminase level above 40 IU/L. The treatment for TB pleuritis is the same as that for pulmonary TB. Tuberculous empyema is a rare occurrence, and the treatment is difficult.

KEY WORDS: Tuberculosis, pleural effusions, adenosine deaminase, gamma interferon, pleural biopsy, empyema

INTRODUCTION

Tuberculosis (TB) remains a major public health problem in developing countries. Most patients with TB have pulmonary TB; however, 25% of adults can present with extrapulmonary TB, which mainly involves the lymph nodes and pleura but can affect any organ system, including the central nervous system (CNS), cardiovascular system, and gastrointestinal (GI) tract [1]. The most common form of extrapulmonary TB is infection of the pleura. In a patient who presents with undiagnosed pleural effusion, the diagnosis of TB pleuritis should be considered. Pleural effusion, as an isolated manifestation of TB, may be self-limited and of little immediate concern, but untreated, it can lead to serious disease many years later.

Pathogenesis and Pathologic Features

Tuberculous pleural effusion may occur in the absence of radiologically apparent TB [2]. The effusion may result as a sequela to a primary infection from 6–12 weeks earlier, or it may represent the reactivation of TB [2]. In developed countries, TB pleural effusions present more often in older patients. The median age in one North American study was 56, suggesting reactivation of the disease [3]. However, a study from 2004 in San Francisco showed that pleural TB cases were 2 times more likely to be clustered (when assessed by genotyping of the mycobacterial organisms) than pulmonary TB and 3 times more likely to be clustered than nonrespiratory TB cases [4]. The observations made in the San Francisco study suggest that the majority of patients has a postprimary infection [4]. This was not confirmed in studies performed in both Houston [5] and Baltimore [6] or in a study in sub-Saharan Africa, in which the prevalence of pleural TB was 63.2% in patients with a primary TB infection [7].

The pathogenesis of TB pleural effusion is thought to be related to the rupture of a subpleural caseous focus in the lung into the pleural space [8]. The basis for this was the observation that a caseous TB focus could be demonstrated in the lung, contiguous with the diseased pleural, in 12 to 15 patients with TB pleuritis [9]. The 3 other patients in this study had parenchymal disease but did not have caseous foci adjacent to the pleura.

Tuberculous pleural effusions are thought to result from a delayed hypersensitivity reaction to mycobacteria and mycobacterial antigens in the pleural space. The resulting inflammation produces lymphocytic pleuritis, which decreases the amount of fluid that can be absorbed from the pleural space. The combination of the extra fluid produced by the inflammation and the decreased lymphatic clearance leads to the accumulation of pleural fluid.

When guinea pigs are immunized to tuberculosis by injecting Freud’s adjuvant containing dead tubercle bacilli in their foot pads, tuberculin (PPD) that is injected into the pleural cavity 3–5 weeks later results in the development of exudative,
predominantly lymphocytic effusion over a period of 24 hours. Antilymphocyte serum that is injected into the pleural space suppresses this effusion [10].

In a model of TB pleurisy, when BCG-sensitized rabbits are given injections with BCG into the pleural space, the resultant pleural effusion contains predominantly neutrophils in the first 24 hours, followed by macrophages peaking at 96 hours, and then lymphocytes [11]. If the animals are made to be neutropenic, the accumulation of pleural fluid and inflammatory cells, particularly macrophages, is decreased. The intrapleural injection of neutrophils into the neutropenic animals restores the response to control levels. The neutrophils in the pleural space appear to secrete a monocyte chemotaxin that recruits monocytes to the pleural space and thereby contribute to the formation of granulomas [12].

**Incidence**

The percentage of patients who have pleural effusions secondary to tuberculosis varies markedly from country to country. A study from 2013 in sub-Saharan Africa confirmed 144 cases of pleural TB out of a total of 984 patients and found it to be the most common form of extrapulmonary TB [7]. A recent study in Spain conducted from 2000-2009 collected 1835 patients with TB pleural effusions. In the 1990s, TB was the most common cause of pleural effusion in their area. Overall, the number of TB pleural effusion cases decreased by 49% over the 10-year study period. However, the proportion of TB pleural effusion cases to the total cases of TB did not change significantly (between 14.3% and 19.3%) and was much higher than that reported in the United States (about 3.6%) [13]. The US study by Baumann et al. looked at patients from 1993-2003 and found that 3.6% of patients with tuberculosis had TB pleuritis. They also reported that the incidence rate of pleural TB cases was also declining over time [14]. However, because pleural fluid cultures are frequently negative, cases of TB pleuritis may be underreported [14]. These differences may also be attributed to different prevalence rates of TB in the general population [13].

Immunocompromised patients are more likely to develop TB than non-immunocompromised patients. Because TB pleuritis is thought to be due to delayed hypersensitivity, one might hypothesize that the percentage of immunocompromised hosts with TB with pleural effusions would be lower than in immunocompetent hosts [15]. However, this does not appear to be the case. In regions, like Zimbabwe, with a high prevalence rate of pleural TB, 85% of patients with TB pleuritis patients are human immunodeficiency virus (HIV)-positive [16]. The percentage of patients with TB pleuritis was higher in HIV-positive patients than in immunocompetent patients in reports from South Africa (38% vs. 20%) [17] and Uganda (23% vs. 11%) [18].

**Clinical Manifestations**

Tuberculous pleuritis usually presents as an acute or subacute illness. Symptoms are present for less than 1 week in 35% of patients and present for less than 1 month in 71% [19]. The most frequent symptoms are cough (~70%), which is usually non-productive, and chest pain (~70%), which is usually pleuritic [2,7]. Most patients are febrile, but approximately 15% will be afebrile [7]. They may also be dyspneic if the effusion is large. If the presentation is less acute, mild chest pain may occur with at most a low-grade fever, nonproductive cough, weight loss, and easy fatigability [7].

Patients with pleural effusions may be younger than those with parenchymal TB. A study in Istanbul, Turkey collected patients with extrapulmonary TB from 1999-2003 and found their mean age to be 35±14 years. These patients most commonly presented with pleurisy (66%) [20]. However, in the United States, patient populations tend to be older, as it is usually caused by reactivation of TB [2]. In a recent study from the US, the mean age of 14,000 patients reported to the Communicable disease Center between 1993 and 2003 was 49.9 years [14].

The effusions caused by TB are usually unilateral and can vary in size. In one series, the effusions occupied more than two-thirds of the hemithorax in 18%, between one-third and two-thirds of the hemithorax in 47%, and less than one-third of the hemithorax in 34% [21]. In another study, TB was the third leading cause of massive effusions, following malignancy and pneumonia [22]. In approximately 20% to 25% of patients with pleural effusions secondary to TB [21,23], coexisting parenchymal disease is visible on the chest radiograph. If chest CT scans are done, approximately 86% will have parenchymal abnormalities [24]. In such patients, the pleural effusion is almost always on the side of the parenchymal infiltrate and invariably indicates active parenchymal disease. On rare occasions, pleural TB can present with pleural-based nodules and thickening [25].

**Clinical Manifestations in HIV-Positive Patients**

Patients who are HIV-positive are more likely to present with fever, cough, and significant weight loss compared to non-HIV-positive patients. HIV-infected patients more commonly present with systemic symptoms, such as fatigue, night sweats, diarrhea, lymphadenopathy, splenomegaly, and hepatomegaly. They are also more likely to have bilateral pleural effusions [16]. They also have a longer duration of illness and a lower incidence of chest pain [26]. Their pleural fluid is more likely to be smear-positive for acid-fast bacilli (AFB), especially when their CD4 count is less than 100 [26].

**Natural History of Untreated Tuberculous Patients**

Without treatment, TB pleuritis is likely to resolve spontaneously; however, the patient frequently develops active TB at a later date [27,28]. A study by Patiala followed all 2816 members of the Finnish Armed Forces who developed pleural effusion between 1939 and 1945 [27]. After following these patients for a period of 7 years, 43% of these men developed TB [27]. Another study in the US followed 141 military personnel from 1940-1944 with a positive tuberculin skin test and pleural effusion [28]. Although the pleural effusions resolved and all other symptoms disappeared within 2-4 months, 92 of the 141 individuals (65%) subsequently developed some form of active TB [28]. The subsequent incidence of TB was comparable
in those whose pleural fluid cultures were initially positive for TB (60%) and in those whose initial cultures were negative (65%) [28]. A recent review article compiled several studies prior to the chemotherapy era (1900-1966) to estimate case fatalities and the duration of disease of smear-positive tuberculosis [29]. They concluded that the rate of life-time case fatalities in untreated smear-positive TB among HIV-negative individuals was about 70% and was about the same for both males and females [29]. These studies underline the importance of making the diagnosis of TB pleuritis.

DIAGNOSIS

Tuberculin Skin Testing

For a patient suspected of having TB pleuritis, the tuberculin skin test is being utilized less and less. This is because a negative test does not rule out the diagnosis of TB pleuritis. In a recent study of 66 patients, 22 were diagnosed with pulmonary TB via the presence of sputum cultures that were positive for TB or via bronchoscopy. Among the 22 patients with pulmonary TB, 9 patients had a negative TB skin test, indicating a positive response rate of only 59.1% [30]. Only 66.5% of the patients had a positive skin test in a series from Spain [21]. A negative skin test occurred in more than half of the patients tested in a second series from Hong Kong [31]. Testing the skin of a patient with a negative tuberculin skin test and TB pleuritis more than 8 weeks after the development of the symptoms will almost always yield a positive result [15]. However, the skin test may remain a negative result if the patient is immunosuppressed with HIV infection or is severely malnourished [15]. Tuberculin skin testing plays no role in the diagnosis of TB pleuritis presently.

Pleural Fluid Analysis

Pleural fluid with tuberculosis is invariably an exudate. Usually, the pleural fluid protein level exceeds 5 g/dL, which suggests TB pleuritis [15]. The majority of patients has greater than 50% of small lymphocytes in their pleural fluid, and some have more than 90% [7, 21]. However, a patient who presents with symptoms for less than 2 weeks in duration is more likely to have predominantly neutrophils in his pleural fluid [19].

Pleural fluid glucose levels with TB pleuritis may be reduced but are usually similar to serum levels. The pleural fluid pH is usually >7.30 but may be lower. Pleural fluid lactic acid dehydrogenase (LDH) levels are usually higher than serum LDH levels.

The presence of mesothelial cells in the pleural fluid of TB pleuritis is rare. Mesothelial cells cover both the visceral and parietal pleura and are present in many transudative and some exudative effusions. However, the intense lymphocytic infiltration that is present in patients with TB pleuritis covers both pleural surfaces and prevents mesothelial cells from entering the pleural space. It has been confirmed by four different studies that pleural fluid from patients with TB rarely contains more than 5% mesothelial cells [32-35]. Because any condition that involves an inflammatory process of the pleural surfaces will be associated with a paucity of mesothelial cells in the pleural space, the absence of mesothelial cells is not diagnostic of TB pleuritis. HIV-infected patients with TB pleuritis can have mesothelial cells in their pleural fluid. One report identified 3 such patients with significant numbers of mesothelial cells in their pleural fluid [36]. All of these patients had CD4 counts below 100 mm3 in their peripheral blood [36].

Adenosine Deaminase

Testing pleural fluid adenosine deaminase (ADA) levels is an easy and inexpensive manner to establish the diagnosis of TB pleuritis [37]. ADA, a predominant T-lymphocyte enzyme, catalyzes the conversion of adenosine and deoxyadenosine to inosine and deoxyinosine, respectively. Adenosine deaminase has two molecular forms, ADA1 and ADA2. ADA1 is ubiquitous and is found in many cells, while ADA2 is produced mainly by monocytes/macrophages [37]. Most of the ADA in pleural effusions secondary to TB is ADA2. This appears to be paradoxical, as ADA1 comes from lymphocytes, which are the predominant cell type found in TB pleural effusions. This suggests that the origin of ADA in pleural fluid is the pleural surface rather than the cells in the pleural fluid. A ratio of ADA1 to total ADA of less than 0.42 may increase the sensitivity and specificity of the ADA measurement slightly in diagnosing TB pleuritis. However, the separation of ADA into its isozymes is not necessary in the vast majority of cases [38].

In an early study from 1983, the authors measured the ADA level in pleural and peritoneal fluid of 221 patients [39]. All patients with a fluid ADA level of greater than 70 U/L had TB, whereas no patient with a fluid ADA level of less than 40 U/L had TB pleuritis [39]. A recent study in Spain retrospectively looked at all consecutive patients with pleural effusion with a diagnostic thoracentesis at Mendaro Hospital from January 1998 to December 2008 [40]. The ADA levels had been determined in all samples. Of the 472 samples, 73 patients were diagnosed with TB pleural effusions (mean prevalence of 15.3%) [41]. They reported that the sensitivity and specificity of ADA in the diagnosis of pleural TB were 89% and 92.7%, respectively [40]. This was similar to the sensitivity and specificity reported in a recent meta-analysis of 63 studies (92% and 90%, respectively) [41].

ADA levels are also elevated in HIV patients, even in those with very low cell counts [42]. It is known that T-lymphocytes play an important role in the pathogenesis of HIV and that the specific activity of ADA is high in T-lymphocytes [43]. In a study by Baba et al. [42], the sensitivity of ADA was not affected by low CD4 counts, nor was there a significant difference in the mean ADA value in patients with lower CD4 counts. Even at CD4 counts of <10 cells/mm3, the ADA level was still above the cut-off value of 30 U/L [42]. This may be due to the higher immune activation in HIV-positive patients with very low CD4 counts [43].

It should be noted that different authors have used different cut-off levels for ADA, ranging between 30 U/L and 70 U/L. A study by Porcel et al. [44] from 2010 analyzed pleural fluid ADA levels in different scenarios, one being pleural fluid with
high lymphocyte counts, which should be suspected of TB. From these samples, an ADA level above 35 U/L had a sensitivity of 93%, a specificity of 90%, a positive likelihood ratio of 10.05, and a negative likelihood ratio of 0.07 for identifying TB effusion [44]. Based on these results, the authors concluded that a cut-off level of 35 U/L is sufficient, assuming that the prevalence of the disease is high, and that in areas where the prevalence of TB is low, a level greater than or equal to 35 U/L may represent a false-positive result. However, due to its maintained high negative predictive value, an ADA level of less than 35 U/L confidently excludes TB [44].

A primary condition other than TB that causes high levels of ADA in pleural fluid is an empyema. This was also observed in the same recent study by Porcel et al. [44] in which ADA activity was found to be significantly higher in patients diagnosed with pleural tuberculosis and patients with complicated parapneumonic effusion/empyema. When the parapneumonic effusions were categorized as non-complicated, complicated, and empyemas, the latter group exhibited the highest ADA concentrations, along with the TB group [44]. Notably, none of these patients had an ADA level exceeding 250 U/L [44]. However, parapneumonic effusions may be easily distinguished from TB pleuritis for two reasons. They have a different clinical picture, and parapneumonic effusions have predominantly neutrophils instead of lymphocytes, typical of TB. High pleural fluid ADA has been reported in malignancies, such as lymphomas (5%), infectious diseases (e.g., brucellosis, Q fever), and connective tissue diseases, such as rheumatoid arthritis, but these presentations are usually less common [45].

In patients with undiagnosed pleural effusion, the pleural fluid ADA level can be used to exclude a diagnosis of TB pleuritis. One study by Ferrer et al. [46] followed 40 patients with undiagnosed pleural effusions and a pleural ADA level below 43 U/L for a mean of 5 years and reported that none of them developed TB. Pleural effusions with a predominance of lymphocytes that are not a result of TB pleuritis usually have pleural fluid ADA levels of less than 40 U/L. Jimenez and colleagues measured pleural fluid ADA levels in 410 lymphocytic non-TB pleural fluid samples and found that the ADA level was above 40 U/L in only 7 patients (1.7%) [47].

In summary, measurement of pleural fluid ADA levels is useful in the diagnosis of TB pleurisy. In patients with lymphocytic pleural effusion, pleural fluid levels of greater than 40 U/L are suggestive of a diagnosis of TB pleuritis, especially in areas with a high prevalence of tuberculosis.

### Interferon-Gamma

Another test useful in differentiating TB effusions from non-TB effusions is the level of pleural fluid γ-interferon. γ-interferon is a cytokine released by activated CD4+ T lymphocytes that increases the mycobactericidal activity of macrophages. A large study from 2003 Villena et al. [48] measured pleural fluid γ-interferon levels in 595 patients, including 82 with TB, and reported that a cut-off level of 3.7 IU/mL yielded a sensitivity of 0.98 and a specificity of 0.98. A second larger meta-analysis of 22 studies that included 782 patients with TB and 1319 patients with non-TB pleural effusions showed that the mean sensitivity of the γ-interferon assay was 89% and that the mean specificity was 97% [49].

It is impossible to establish a cut-off value overall, as the units and methods of the measurement of γ-interferon levels differ from study to study [45]. A previous meta-analysis that looked at 13 studies on γ-interferon and ADA that included 1189 patients concluded that both γ-interferon and ADA are accurate in diagnosing TB pleuritis [50]. In this study, the pooled overall sensitivity and specificity from the meta-analysis were 93% for ADA and 96% for γ-interferon [50]. In summary, the long historical success of ADA and the fact that it is simpler and cheaper than the γ-interferon test makes it the preferred test.

### Gamma Interferon Release Assays

γ-interferon release assays (IGRAs) are T-cell-based in vitro assays that measure γ-interferon release by sensitized T-cells from peripheral blood or pleural fluid. T-cells will secrete γ-interferon when they react with highly specific Mycobacterium tuberculosis-specific antigens, such as early secretory antigen (ESAT)-6 and culture filtrate protein (CFP)-10 [45]. QuantiFERON-TB Gold and T-SPOT.TB are the only currently available IGRAs. These tests can be used to accurately identify patients who have been infected with M. tuberculosis. However, they are not as helpful in identifying patients with pleural TB. A recent meta-analysis of 7 studies that included 213 patients with TB pleural effusions found the sensitivity and specificity of IGRA measurements in pleural fluid to be 0.75 and 0.82, respectively [51]. Moreover, another study showed that measuring γ-interferon levels in pleural fluid was superior to IGRA in regards to both sensitivity and specificity [52]. Using IGRAs for blood or pleural fluid is not recommended for making a diagnosis of TB pleuritis [53].

### Polymerase Chain Reaction

One way to directly and quickly detect the presence of M. tuberculosis in clinical specimens, such as pleural fluid, is to use polymerase chain reaction tests or other nucleic acid amplification (NAAT) assays. These tests amplify M. tuberculosis-specific nucleic acid sequences with a nucleic acid. There are two widely available assays, the Amplicor Mycobacterium tuberculosis test (developed by Amplicor) and the Amplified Mycobacterium tuberculosis Direct test (MTD, developed by Gene-probe) [54]. A recent study found that the NAATs were specific but not necessarily sensitive in identifying M. tuberculosis in patients who were HIV-positive with negative sputum smears [55]. The use of pleural fluid NAAT tests was evaluated in a meta-analysis of 20 studies that concluded that these tests demonstrated high specificity (97% for commercial and 91% for in-house tests) but also poor sensitivity (62% for commercial and 76.5% for in-house tests) [56]. The low sensitivity of the NAAT tests might be due to the presence of inhibitors in the pleural fluid or to intracellular sequestration of the mycobacteria. Currently, the use of NAAT tests in the diagnosis of TB pleurisy should be limited to investigational studies.
Xpert MTB/RIF (GeneXpert) is a newly developed NAAT test that has been designed to test for *Mycobacterium tuberculosis* (MTB) and rifampin resistance (RIF). It uses a hemi-nested real-time PCR assay to amplify an MTB-specific sequence of the rpoB gene, which is probed with molecular beacons for mutations in the rifampin resistance-determining region [57]. This test can yield results in 2 hours. A study from 2010 by Boehme et al. [58] evaluated the sensitivity and specificity of Xpert MTB/RIF for the diagnosis of tuberculosis as compared to sputum smears and culture. Among patients with culture-positive TB, the overall sensitivity of the Xpert MTB/RIF assay was 97.6% [58]. The sensitivity was 99.8% for smear- and culture-positive cases and 90.2% for smear-negative and culture-positive patients [58]. The estimated specificity for a single direct Xpert MTB/RIF assay on sputum was 99.2% [58]. The authors concluded that the Xpert MTB/RIF assay provides sensitive detection of tuberculosis and also rifampin resistance from untreated sputum in less than 2 hours [58]. However, using the Xpert MTB/RIF assay to diagnose TB pleuritis from pleural fluid samples has only been described in one study so far, by Hillemann et al. [59]. In this study, 113 pleural fluid samples were collected from patients with suspected or non-suspected clinical TB, and they found the sensitivity to be 98.1%, but the specificity was not able to be calculated [59]. Because of the lack of literature and randomized control trials on the efficacy of the Xpert MTB/RIF assay for the detection of pleural TB, we do not recommend the use of this test as a diagnostic modality at this time.

**Sputum Smears and Cultures**

Examination of sputum for mycobacteria is one test that is frequently overlooked in the diagnostic work-up of patients with undiagnosed pleural effusion. The diagnostic yield of mycobacterial smears and cultures was evaluated by Conde et al. [60] in 84 patients with TB pleuritis. They induced sputum in those unable to spontaneously expectorate. Sputum studies were found to be positive in 44 out of the 84 patients (52%) [60]. Of those 44 patients, 10 patients had positive sputum smears, whereas cultures were positive in all [60]. In patients with a normal chest radiograph except for pleural effusion and in whom sputum was induced, the sputum was positive in 35 out of 64 patients (55%) [60]. This study indicates that sputum should routinely be obtained for mycobacterial smears and cultures when TB pleuritis is suspected.

**Pleural Fluid Stain and Culture**

Pleural fluid smears for mycobacteria in immunocompetent patients are not routinely indicated, because they are almost always negative, unless the patient has a TB empyema [21,61]. Cultures of pleural fluid should be taken, but in most series, the cultures are positive in less than 40% of immunocompetent patients [7,20]. Smears should be obtained in immunocompromised hosts, as they are positive in about 20% of HIV-positive individuals [26]. For mycobacterial cultures, the use of the BACTEC system (liquid cultures) with bedside inoculation provides higher yields and faster results than Lowenstein-Jensen medium (solid cultures). In one study, the median time for BACTEC cultures to become positive was 18 days (range 3-40 days), as compared to 33.5 days (range 21-48 days) for Lowenstein-Jensen cultures [62]. In a second study, pleural fluid cultures were positive by the BACTEC system in 24% of HIV-negative and 75% of HIV-positive individuals, whereas the cultures were positive by Lowenstein-Jensen medium in 12% of HIV-negative patients and 56% of HIV-positive patients [63].

**Pleural Biopsy**

Blind needle biopsy of pleura has been the most common way to make the diagnosis of TB pleuritis for over the last 50 years. The diagnosis of TB pleuritis can be made with the demonstration of granuloma in the parietal pleura; caseous necrosis and AFB are not necessary for the diagnosis. Although other disorders may cause granuloma formation, such as fungal diseases, sarcoidosis, and rheumatoid pleuritis, more than 95% of patients with granulomatous pleuritis have TB [15]. The biopsy specimen should also be sent for an AFB smear and cultured for *M. tuberculosis*, even if there are no granulomas present. In a study of 248 patients with TB pleuritis who underwent needle biopsy of the pleura, the biopsy showed granulomas in 198 patients (80%), the AFB stain of the biopsy was positive in 64 patients (25.8%), and the culture of the biopsy tissue was positive in 140 patients (91%) [21].

Another way to collect pleural tissue is thoracoscopy, but this procedure is usually not necessary to make the diagnosis of TB pleuritis. If the clinical picture is confusing, thoracoscopy is sometimes indicated. If the patient does have TB pleuritis, thoracoscopy will establish the diagnosis in nearly 100% of cases [64].

**TREATMENT**

**Chemotherapy**

The current recommendations for TB, pulmonary and extrapulmonary, are as follows [65,66]. The 6-month treatment regimen usually consists of a 2-month period of isoniazid (INH), rifampin, and pyrazinamide. Ethambutol is included in the initial regimen until the results of drug susceptibility studies are available, unless there is a low risk of drug resistance. The next phase of the treatment should be INH and rifampin for 4 months. Directly observed therapy (DOT) is recommended. It is also possible to use 9-month therapy of INH and rifampin if the organisms are fully susceptible to the drug.

The recommendations above may be somewhat intensive for patients with isolated TB pleuritis, as they tend to have a relatively low mycobacterial burden. The main pathophysiologic abnormality is hypersensitivity. INH and rifampin only were used to treat patients with isolated TB pleuritis in two different studies [67,68]. The first, by Canete et al. [67], treated 130 patients with 5 mg/kg of INH and 10 mg/kg of rifampin daily for 6 months and reported no treatment failure. The second, by Dutt et al. [68], treated 198 patients with 300 mg INH and 600 mg rifampin daily for 1 month, followed by 900 mg INH plus 600 mg rifampin twice a week for the next 5 months and reported only 1 failure. However, no guidelines recommend only two-drug therapy.

With treatment, the patient’s symptoms and radiologic changes gradually subside. Typically, a patient becomes afebrile within 2 weeks, but fever can persist as long as 2
months [69]. Initiating anti-TB therapy at the same time that a therapeutic thoracentesis is performed results in most patients becoming afebrile within 5 days [70,71]. Pleural fluid resorbs in an average of about 6 weeks but can last as long as 12 weeks [69]. The patient does not require bed rest and only needs to be isolated if his sputum is positive for mycobacteria.

Residual pleural thickening may occur in approximately 50% of patients 6-12 months after initiating therapy [72]. The pleural thickening may result in a reduction in vital capacity. At the end of their TB treatment, the FVC was less than 80% of the predicted value in 8 of 81 patients (10%) in one study [73]. However, this study showed only a weak correlation (r=-0.298) between the degree of pleural thickening and the reduction in FVC [69]. Patients with low pleural fluid glucose, a high pleural fluid LDH level, and high pleural cytokine levels are likely to have a higher incidence of pleural thickening [72,74]. In a randomized controlled study of 52 patients, the administration of 2.5 mL of a hyaluronate-based gel resulted in significantly faster fluid absorption and significantly less pleural thickening at 3 months (0.57 cm vs. 1.14 cm) [75]. Residual pleural thickening is more common if the fluid is initially loculated [76].

Attempting to completely remove all pleural fluid does not appear to reduce the amount of residual pleural thickening. In a study where 61 patients were randomized to receive pigtail drainage until the drainage was less than 50 mL/day or until there was no drainage, the residual pleural thickening was basically identical in both groups [77]. It should be noted that the duration of dyspnea was significantly shortened by the use of pigtail drainage by a median of 4 days versus 8 days.

The degree of residual pleural thickening in patients with loculated pleural effusion may be decreased by the administration of a fibrinolytic. Kwak and associates randomized 43 patients with loculated pleural effusions to receive 100,000 IU urokinase daily, administered through a pigtail catheter, starting when the pleural fluid drainage was less than 100 mL/day and finishing when the amount of pleural fluid was less than 50 mL/day, or only anti-TB therapy [78]. They concluded that the mean width of pleural thickening was 0.46 cm in the urokinase group and 1.86 cm in the control group [78].

After initiation of anti-TB therapy, paradoxical worsening can occur in some patients. In a study of 61 patients on standard therapy with INH, rifampin, pyrazinamide, and ethambutol, 10 patients (17%) had an increase in the size of their effusion after therapy was initiated [79]. This study suggests that this may be due to immune rebound, by which the improved cell-mediated immunity after treatment coincided with excessive antigen load resulting from rapid bacterial lysis [79]. Some patients with TB pleuritis can develop a peripheral nodule during treatment [80]. These nodules usually represent pulmonary TB and disappear as the anti-TB therapy is continued [80].

During the treatment course of pulmonary TB, some patients may develop pleural effusion. One study found 29 patients who developed pleural effusions while receiving chemotherapy for pulmonary (16 patients) or extra-pulmonary TB (13 patients) [81]. The effusion developed between the 5th and 8th weeks of starting chemotherapy in 13 patients, between the 9th and 15th weeks in 9 patients, and between the 13th and 25th weeks in 5 patients [81]. Interestingly, the pleural fluid was found to be exudative in all cases, and cultures for M. tuberculosis were positive in 4 patients. Most patients responded to the same chemotherapy regimen without interruption [81].

**Corticosteroids**

The use of corticosteroids in the treatment of TB pleurisy remains controversial. There are two controlled studies in which therapeutic thoracentesis was performed, and there were no benefits observed [70,71]. In a third study in which no therapeutic thoracentesis was performed, the duration of fever and the time required for fluid resorption were reduced [82]. The degree of residual pleural thickening is not reduced with the administration of corticosteroids. The administration of prednisolone was associated with an increased risk of Kaposi sarcoma in a study of HIV patients with associated pleural TB [83]. At this time, there are insufficient data to support evidence-based recommendations, as outlined in a recent Cochrane review regarding the use of adjunctive corticosteroids in patients with TB pleurisy [84].

The recommended treatment of a patient with TB pleuritis with adjunctive steroids is as follows. A therapeutic thoracentesis is recommended if the patient is more than mildly symptomatic. However, if the patient continues to have severe systemic symptoms (fever, malaise, pleuritic chest pain) after the thoracentesis, the administration of 80 mg of prednisone every other day until the acute symptoms have abated is recommended. Thereafter, the steroids are rapidly tapered.

**Tuberculous Empyema**

Tuberculous empyema is a rare occurrence characterized by purulent pleural fluid that is loaded with TB organisms on AFB stains [85]. It usually develops in fibrous scar tissue resulting from pleurisy, artificial pneumothorax, or thoracoplasty [86]. A case series from Italy observed 110 cases of patients hospitalized with long-term disabling sequelae of pulmonary tuberculosis. Twelve patients suffered from post-TB chronic empyema with a mean latency period of about 44 years between the acute TB illness and clinical presentation of the empyema. Of these 12 patients, 9 had received artificial pneumothorax therapy, 1 had received a thoracoscopy, and 2 had received inadequate anti-TB therapy [86]. The underlying pleura is frequently heavily calcified, and the patient presents with a subacute or chronic illness characterized by fatigue, low-grade fever, and weight loss. There are rare occasions where a TB empyema produces empyema necessitatis, where the empyema ruptures through the chest wall [87]. In fact, TB is the most common cause of empyema necessitatis [87]. The chest radiograph may show obvious pleural effusion but frequently only shows evidence of pleural thickening. The chest CT scan usually demonstrates a thick, calcific pleural rind and rib thickening surrounding loculated pleural fluid. The diagnosis is established with a diagnostic thoracentesis, which yields thick pus on which the AFB smear is markedly positive.
Treatment is difficult, and decortication, extrapleural pneumonectomy, and thoracoplasty have all been recommended. All of these procedures have substantial morbidity and some mortality, usually because of the compromised respiratory status of the patient. The initial approach involves intensive chemotherapy with serial thoracentesis, as this can be curative at times [88]. It is important to use a multiple (three or more)-drug regimen and to employ agents at their maximal tolerated dosages, because these patients have a strong tendency to develop resistant organisms. This is probably because the anti-TB drugs frequently do not reach their normal levels in the pleural space, owing to the thick, fibrous, and often calcified pleura [89].

Expert Commentary- Recommended Approach to a Patient with Undiagnosed Pleural Effusion

The diagnosis of TB pleuritis should be considered when a patient presents with new pleural effusion. If the diagnosis is not made, the patient is at risk for developing pulmonary or extrapulmonary tuberculosis. At the time of the initial thoracentesis, the pleural fluid should be analyzed for the differential cell count and ADA level, and the fluid should be cultured for mycobacteria. If the pleural fluid has a lymphocyte-to-neutrophil ratio of greater than 0.75 and an ADA level above 70 U/L, the diagnosis of TB pleuritis is virtually established. If the patient has a lymphocyte-to-neutrophil ratio of greater than 0.75 and the pleural fluid ADA is between 40 and 70 U/L, one can assume that the diagnosis of TB pleuritis has been made. If the patient’s clinical picture is not typical for TB pleuritis, consider performing a needle biopsy of the pleura or a thoracoscopy. If the pleural fluid ADA level is below 40 U/L, the diagnosis of TB is unlikely. However, if the patient has a clinical picture typical of TB pleuritis and, particularly, if the pleural fluid has a high lymphocyte count, the possibility of TB pleuritis can be further evaluated by needle biopsy of the pleura or thoracoscopy [15].

Another way to diagnose TB pleuritis would include the gamma-interferon level of the pleural fluid. Studies have shown that pleural fluid levels of both ADA and interferon-gamma are reasonably accurate at diagnosing TB pleuritis, with a joint sensitivity and specificity of 93% for ADA and 96% for interferon-gamma [90]. However, the measurement of ADA level is preferred, because it is less expensive. Because no culture results are obtained and because the sensitivities of the organism cannot be determined, there are some that argue against relying primarily on the ADA level in the pleural fluid to make a diagnosis of TB. It should be noted that while the pleural biopsy is positive in only 55%, cultures of the pleural fluid itself are positive in 35%. Therefore, performing a pleural biopsy only increases the overall percentage of a TB diagnosis by about 20%, which may not be worthwhile [15].

Five-Year View

We expect that there will be limited evolution in TB pleural effusions over the next 5 years. One problem that might arise is the occurrence of more and more drug-resistant TB pleuritis. One possible advance in the diagnosis of TB pleuritis may be the development of cheaper and easier interferon-gamma assays. A second advance may be the development of nucleic acid amplification assays with greater sensitivity for the diagnosis of TB pleuritis. It might be worthwhile to determine how sensitive the Xpert MTB/RIF assay is in diagnosing TB pleuritis from pleural fluid, as this could potentially be a cheap and quick way to make the diagnosis.

Key Issues

- Tuberculous pleural effusions should be diagnosed and treated, because if the diagnosis is not made, the patient is at risk for developing pulmonary or extrapulmonary TB.
- Patients who are HIV-positive have a higher incidence of pleural tuberculosis.
- The presentation of TB pleuritis is usually an acute illness with fever, cough, and pleuritic chest pain.
- Pleural fluid is an exudate that often has a predominance of lymphocytes.
- Cultures of pleural fluid are positive for Mycobacterium tuberculosis in less than 40%, and smears are virtually always negative.
- One method that can be used to diagnose TB effusion is to demonstrate a pleural fluid adenosine deaminase level above 40 U/L in a patient with lymphocytic pleural effusion.
- Chemotherapy for tuberculosis is the same as that for pulmonary TB.

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