Tuberculous pleural effusions: advances and controversies

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Abstract: On a global scale, tuberculosis (TB) remains one of the most frequent causes of pleural effusions. Our understanding of the pathogenesis of the disease has evolved and what was once thought to be an effusion as a result of a pure delayed hypersensitivity reaction is now believed to be the consequence of direct infection of the pleural space with a cascade of events including an immunological response. Pulmonary involvement is more common than previously believed and induced sputum, which is grossly underutilised, can be diagnostic in approximately 50%. The gold standard for the diagnosis of tuberculous pleuritis remains the detection of *Mycobacterium tuberculosis* in pleural fluid, or pleural biopsy specimens, either by microscopy and/or culture, or the histological demonstration of caseating granulomas in the pleura along with acid fast bacilli (AFB). In high burden settings, however, the diagnosis is frequently inferred in patients who present with a lymphocytic predominant exudate and a high adenosine deaminase (ADA) level, which is a valuable adjunct in the diagnostic evaluation. ADA is generally readily accessible, and together with lymphocyte predominance justifies treatment initiation in patients with a high pre-test probability. Still, false-negative and false-positive results remain an issue. When adding closed pleural biopsy to ADA and lymphocyte count, diagnostic accuracy approaches that of thoracoscopy. The role of other biomarkers is less well described. Early pleural drainage may have a role in selected cases, but more research is required to validate its use and to define the subpopulation that may benefit from such interventions.

Keywords: Pleural effusion; tuberculosis (TB); thoracentesis; pleural biopsy

Introduction

Mycobacterium tuberculosis (*M. tuberculosis*) is a pathogenic bacterial species in the family Mycobacteriaceae and the causative agent of most cases of tuberculosis (TB) (1). Despite being isolated by Robert Koch in 1882, as well as the availability of effective treatment and the use of a live attenuated vaccine in many parts of the world, TB remains one of the deadliest communicable diseases. In 2013, an estimated 9 million people developed active TB, with 1.5 million deaths attributed to the disease (2). According to the World Health Organisation the incidence of pulmonary TB in some regions is as high as 1,000 cases per 100,000 persons (2). Although TB affects the lungs in the majority of patients, extrapulmonary TB serves as the initial presentation in about 25% of adults, and primarily involves

the lymph nodes and pleura (3). This review gives an overview of the pathogenesis, clinical presentation, diagnosis and treatment of TB pleural effusions, highlighting recent advances and controversies.

Pathogenesis

Until recently TB pleural effusions were thought to occur largely as a result of a delayed hypersensitivity reaction. Injecting tuberculin into the pleural cavity of guinea-pigs sensitized with heat killed *M. tuberculosis*, produces a large protein-rich pleural effusion over a 24-hour period, which is completely suppressed by antilymphocyte serum (4). Based on this model and the fact that researchers were unable to culture *M. tuberculosis* from pleural fluids, the pathogenesis was presumed to be due to delayed hypersensitivity rather

than a direct infection of the pleural space. With the advent of improved culture media it is now possible to culture *M. tuberculosis* from both pleural fluid and pleural tissue in as many as 70% of cases (5), and following Koch's postulate for infection, this would suggest a causal relationship (6).

The pleural effusion is likely a manifestation of paucibacillary mycobacterial infection within the pleural space, which is acquired from initial parenchymal lesions and results in an immunological response that both increases pleural fluid formation and decreases pleural fluid removal (7). Initially, there is a rapid neutrophilic inflammatory response within the pleura which is symptomatic. This is followed by a protracted lymphocyte driven immune reaction which is accompanied by pleural granuloma formation and release of adenosine deaminase (ADA). It is therefore plausible that the likelihood of a positive pleural fluid culture decreases with time, as the effusion becomes lymphocyte predominant, and viable mycobacteria are contained.

Similar to lung parenchymal TB, the pathogenetic hypothesis of pleural TB suggests that a strong T-helper type 1 (Th1)-like immunity (interferon dominant) is essential for the containment of *M. tuberculosis*, while these protective effects are antagonized by T-helper type 2 cytokines, primarily interleukin (IL)-4 (8). Activated CD3+ and CD4+ Th1 cells, through the release of interferon gamma (IFN-γ) and other Th1 cytokines, activate macrophages to kill *M. tuberculosis*, whereas Th2 cytokines may antagonize this effect (9). The predominance of Th1 immunity in TB pleural effusions is confirmed by the high levels of IFN-γ, and other inflammatory cytokines (e.g., IL 12), while the proportion of helper T-cells in pleural fluid are also elevated compared with serum or peripheral blood (8,10,11), thus creating a compartmentalised pleural space. The frequency of IL-4 producing T-cells, representing Th2 immunity, is significantly lower in pleural fluid compared to peripheral blood (8). This compartmentalisation may not occur immediately after infection, as shown by animal and *in vitro* studies (12,13). Polymorphonuclear leukocytes are the first cells to respond, remaining the predominant cells for the first 24 hours, and are then followed by macrophages, which peak at 96 hours, and then by lymphocytes. It seems the polymorphonuclear leukocyte influx is a specific response to pleural injury and, either through itself or its interaction with the macrophage, plays a role in host defence mechanisms against the tubercle bacilli (12,13).

Clinical manifestations

Pleural is second only to lymphatic involvement as a site of

extrapulmonary TB (7,14), and may occur in either primary or reactivation disease (15,16). In the USA 3-5% of TB patients are reported to have pleural disease (14), while the incidence of pleural involvement may be as high as 30% in high-burden TB settings (17,18). Where HIV is endemic, TB pleuritis is the most common cause of a lymphocytic effusion and thought to be caused by primary infection in 30% of patients (18). Most (HIV negative) patients with TB pleural effusions will present with an acute febrile illness characterised by a non-productive cough and pleuritic chest pain, but without an elevation in the peripheral white blood cell count (7,19). Night sweats, chills, weakness, dyspnoea, and weight loss are also frequently reported (20). TB pleural effusion may resolve spontaneously without treatment, but patients frequently develop active TB at a later date (21). In non-HIV endemic areas where reactivation is the predominant mechanism of TB disease, pleural involvement is reported to occur in 4% of cases. Such patients have a more insidious onset, are of older age and are more likely to be immunocompromised (18). Immunocompromised patients have been shown to have higher positive culture rates, thought to be due to impaired clearing of the organism (22).

Chronic TB empyema is less common, and represents a distinct entity of chronic, active infection within the pleural space. It is characterised by purulent fluid where virtually all the nucleated white blood cells are neutrophils, and can occur in several settings: (I) progression of a primary TB pleuritis; (II) direct extension of infection into the pleural space from thoracic lymph nodes or a subdiaphragmatic focus; (III) haematogenous spread; or (IV) following pneumonectomy (9). The majority of empyemas will resolve leaving a thickened, scarred, and calcified pleura (23). However, this process may be complicated by decompression through the chest wall (empyema necessitans) (24). Pneumothorax secondary to TB often heralds severe pulmonary involvement by the infectious process and the onset of bronchopleural fistula and empyema (23).

Pleural fibrosis or fibrothorax (*Figure 1*) is a well described complication of TB pleuritis (25). However, uncertainty remains to the exact prevalence, with reports varying between 5% and 55% (26,27). Further, pleural fibrosis may have long term clinical implications, with some studies reporting the association of residual pleural thickening (≥10 mm) with significant morbidity, including chronic chest pain, dyspnoea as well as impairment in lung function (25,28).
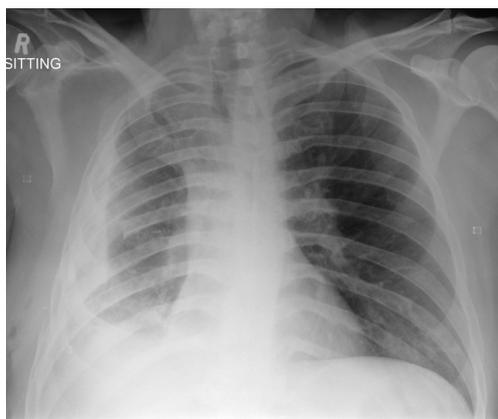

Figure 1 This chest radiograph demonstrates a severe case of fibrothorax as a long-term complication of TB pleuritis. TB, tuberculosis.
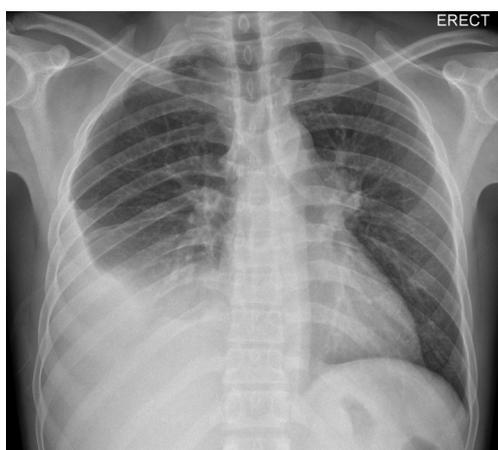

Figure 2 This chest radiograph was obtained from a patient with confirmed pleural TB. No significant parenchymal changes could be observed. TB, tuberculosis.

Chest X-ray

Pleural effusions secondary to TB are largely unilateral with a slight right-sided predominance, reported to occur in 55% of cases (*Figure 2*) (29). The effusions are typically small to moderate in size, occupying less than one-third of the hemithorax in approximately 80% of cases (29). However, neither the size nor side of the effusion has been reported to have bearing on prognosis (30).

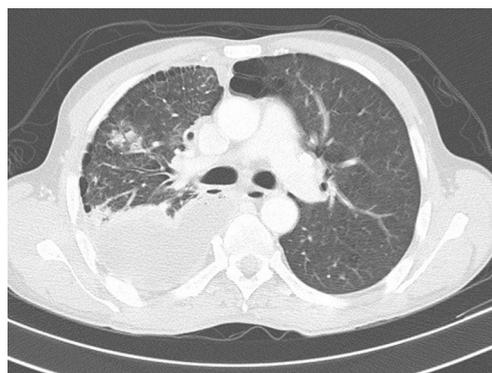The coexistence of parenchymal disease in association with pleural effusion has been observed on chest radiograph

Figure 3 A CT from a patient with confirmed TB pleural effusion with parenchymal involvement (sub-segmental consolidation in this particular case). CT, computed tomography; TB, tuberculosis.

in up to 50% of patients (7), and occurs on the same side in almost all cases (20). Observed parenchymal changes are located in the upper lobes in three quarters of cases, suggesting reactivation as the cause of TB. In the remaining patients, parenchymal disease is located in the lower lobe suggesting primary TB infection (20).

Ultrasonography

Thoracic ultrasound is now accepted as standard of care in performing thoracentesis and closed pleural biopsies (31). Detection of localised pleural thickening and other pleural abnormalities can direct the operator to a preferred biopsy site (32). However, apart from the performance of invasive diagnostic procedures, ultrasound may additionally assist in characterising the nature of the effusion (31). The ultrasonographic appearance of pleural effusions secondary to TB range from anechoic to complex septated or non-septated to even homogeneously echogenic effsuions (33,34).

Computed tomography (CT)

CT of the chest is currently the best imaging modality to visualise both pleura and lung parenchyma in TB pleural effusions (*Figure 3*). Apart from visualising the extent of the disease, CT can be used to assess TB empyema, which can be divided into three distinct phases. The exudative phase represents the initial uncomplicated effusion, followed by the fibrinopurulent phase, where CT typically shows thickened visceral and parietal pleurae separated by fluid, known as the "split pleura" sign. In the organizing phase, CT reveals a loculated pleural fluid collection with a

thickened pleural peel and variable degree of calcification with or without proliferation of extrapleural fat (24).

CT is more sensitive in diagnosing coexistence of parenchymal abnormalities when compared to conventional chest radiographs. In a recent study, more than 80% of patients had pulmonary parenchymal abnormalities when CT scanning was performed (35). The most common CT findings being micronodules in both the subpleural and peribronchovascular interstitium, with interlobular septal thickening, suggesting lymphatic spread of TB (35). Interestingly, in addition to these findings, a paradoxical response to treatment is not rare in patients with pleural TB, and is noted especially in young, previously healthy, male patients with subpleural nodules on initial CT scans (35).

Diagnosis

Principles

The gold standard for the diagnosis of TB pleuritis is detection of *M. tuberculosis* in the sputum, pleural fluid or pleural biopsy specimens, either by microscopy and/or culture, or the histological demonstration of caseating granulomas in the pleura along with acid fast bacilli (AFB) (18,28,34). In high burden settings, however, the diagnosis is frequently inferred in patients who present with a lymphocytic predominant exudate and high ADA level.

Sputum

It was previously believed that patients without overt coexisting parenchymal lesion are sputum negative and, therefore, noncontagious. Moreover, the mycobacterial culture rate in non-induced sputum is low. Reported sensitivities range from 0% to 30% (36). The method of sputum collection, however, is of crucial importance. Conde *et al.* (37) reported a yield of 52% on mycobacterial culture with induced single sputum specimens. Even in patients with normal underlying lung parenchyma on chest X-ray, the yield of sputum culture in induced samples approached 55%. Therefore, in patients with suspected TB pleural effusion it is important to obtain cultures on induced sputum samples, even in the absence of obvious parenchymal involvement. To our knowledge there are no studies evaluating the role of sputum nucleic acid amplification (NAA) molecular studies such as Xpert MTB/RIF in the context of TB pleural effusions. NAA tests

may increase the diagnostic yield of sputum compared with conventional microscopy, but is unlikely to be more sensitive than culture.

Thoracentesis

Microscopy and culture

The macroscopic appearance is that of straw coloured fluid in more than 80% of cases (5). Microscopy for AFB in the pleural fluid can identify *M. tuberculosis* in fewer than 10% of cases. The exception to this is patients with HIV and tuberculous empyema, where yields may be higher (>20%) (9). Culture of the pleural fluid can be performed on either solid or liquid media as in the commercially available and widely used BACTEC MGIT semi-automated system (Becton-Dickinson, Franklin Lakes, NJ, USA), or with manual culture methods that might allow resistance testing at the same time such as the microscopic-observation drug susceptibility (MODS) assay (38). When using solid culture media, sensitivities reported have been low, in the range of 12% to 30%. However, it appears that liquid culture media display better sensitivities of up to 70%. A further benefit of using liquid media is the significantly shorter time required for culture results, being 2 weeks compared to the traditional 6 weeks for solid media (39).

Perhaps counter-intuitively, it does not appear that sending larger volumes of pleural fluid for culture improves diagnostic sensitivity. von Groote-Bidlingmaier *et al.* compared the yield of high and low pleural fluid volumes (100 *vs*. 5 mL) inoculated into liquid culture medium in patients with a high pre-test probability of TB (22). It was shown that the absolute yield was not significantly higher for the larger volume (53.5% *vs*. 50% respectively; P=0.75). In the same study, HIV-positive individuals had culture-positive pleural fluid more frequently than HIV-negative patients. This is presumably due to impaired bacterial clearance from the pleural space. Underlying immunosuppression as a contributor is corroborated by the known negative association of lymphocyte percentage in pleural fluid with the probability of positive culture of pleural fluid (5). The combination of pleural fluid and sputum cultures in the diagnostic workup of TB pleuritis seems a reasonable initial approach, with a combined diagnostic yield of almost 80% (5,22). In a recent study the reported diagnostic yield was 63% for effusion culture, 48% for sputum culture and 79% for the combination of effusion and sputum cultures, using liquid culture media (5).

Routine chemistry

The effusion is uniformly exudative having protein concentrations invariably >50, and >30 g/L in 50% to 77% of cases (40). The pleural fluid lactate dehydrogenase (LDH) level is elevated in approximately 75% of cases, with levels commonly exceeding 500 IU/L (7,20,40). The pleural fluid pH is usually less than 7.40 with values below 7.30 in about 20% of cases (20,40). A low pH and a low glucose concentration may be observed but are more characteristic of chronic tuberculous empyema than TB (41,42). In fact, a pleural fluid pH of <7.20 indicates a possible empyema, prompting the physician to consider drainage of the fluid. The pleural fluid glucose concentration in TB is normally between 3.3 and 5.6 mmol/L, with glucose levels <2.8 mmol/L seen in 7-20% of effusions, while extremely low glucose concentrations (<1.7 mmol/L) may occasionally be observed (20,40).

Adenosine deaminase (ADA)

ADA levels are most useful when there is a moderate to high suspicion of TB in patients with negative pleural fluid or biopsy cultures, and non-diagnostic histology (43). There is a wide range of cut-off values used by authors but in the majority of studies the most accurate threshold was found to range between 40 and 60 U/L (43). In a study of 254 patients with pleural TB, 99.6% had ADA more than 47 U/L (29) and in another group of 303 patients in a high TB prevalence population with exudative effusions, 58% had TB with a lymphocytic predominant effusion and ADA more than 50 U/L (44). The diagnostic usefulness of ADA depends not only on its sensitivity and specificity, but also on the local prevalence of TB. In populations with a high prevalence of TB and clinical suspicion of TB effusion, elevated ADA level might be considered as a confirmatory test justifying treatment initiation. In contrast, in countries with a low prevalence of TB, the negative predictive value remains high even though the positive predictive value of pleural ADA declines. This was illustrated by two studies done in populations with low TB prevalence and non-TB lymphocytic effusions, in which 97% and 98% had ADA levels less than 40 U/L (45,46). Therefore, a negative ADA test may justify abandoning further diagnostic procedures for TB, and pursuing alternative diagnoses.

When interpreting ADA levels, the clinician must additionally be aware of situations which may increase the likelihood of both the false-negative and false-positive ADA results. In the early phase of the disease low levels of ADA in the pleural fluid may be found, giving rise to a false negative result. However, ADA levels will invariably be elevated if thoracentesis is repeated a few days later (47). Additional care should also be taken when interpreting pleural ADA levels in elderly patients and/or current smokers, as ADA levels may be low in such TB patients (48). Conversely, raised ADA levels may be observed in a number of conditions potentially leading to a false positive diagnosis of TB. These include rheumatoid effusion, empyema due to other bacteria, mesothelioma, lung cancer, parapneumonic effusion, and haematological malignancies (47,48).

The diagnostic accuracy of ADA can be improved by measuring different ADA isoenzymes. ADA-2 is increased in TB effusions, while ADA-1 is increased in other bacterial empyemas (49), and distinguishing between these two principal isoenzymes can increase the specificity of ADA for diagnosing TB. Use of the ADA-2 isoenzyme measurement increased the specificity for TB from 91% to 96% (50) and 92.1% to 98.6% (51), in two different studies.

Although it has been suggested that ADA might be a less sensitive marker of TB in immunocompromised patients, there is currently little evidence to support this view. Baba *et al*. (52) demonstrated that ADA is a reliable marker of pleural TB in HIV-positive patients, even for those with low CD_4 counts, while Chung *et al*. (53) confirmed that ADA is an accurate marker in renal transplant recipients.

Nucleated cell count and cytology

The cell count performed usually reveals a nucleated (white) cell count between 1,000 and 6,000 cells/mm^3 (29), and has a T lymphocyte predominance in 60% to 90% of cases (7,20,40). However, the predominant nucleated cell type can vary depending on timing of collection of the pleural fluid. Fluid collected in the first few days may exhibit a neutrophil predominant effusion, while lymphocytes tend to dominate thereafter (12,13). A lymphocytic predominant effusion may be defined as one with more than 75% lymphocytes and/or a lymphocyte to neutrophil ratio more than 0.75 (18). When a lymphocyte neutrophil ratio of 0.75 or greater is used in combination with ADA, the sensitivity, specificity, positive predictive value, negative predictive value, and efficiency for the identification of TB were reported at 88%, 95%, 95%, 88%, and 92%, respectively (44). Other cell types are much less common in TB pleural effusions, with eosinophils being rare unless the patient has had a pneumothorax or haemothorax near the time of pleural analysis (54). The presence of more than 5% mesothelial cells is unusual (55). Cytological examination of the pleural fluid is routinely done, as previously stated, as a malignant

pleural effusion (MPE) may present with a lymphocytic predominant exudate as well as a high ADA.

Additional pleural fluid assays and biomarkers

IFN-γ is an important Th1 cytokine and is important in the host's immune response to mycobacterial infection. Measurement of unstimulated pleural fluid IFN-γ concentration by commercially available enzyme-linked immunosorbent assay kits is considered a useful diagnostic tool to diagnose TB pleuritis (49,56). However, concerns similar to that for ADA around the specificity of the test have been expressed. In one study including 145 patients with TB, an IFN-γ concentration >140 pg/mL had sensitivity and specificity of 94% and 92%, respectively (29), while another study (n=66) of exudative, lymphocytic pleural effusions using a cut-off value of 240 pg/mL, found a sensitivity and specificity of 95% and 96% (57). A meta-analysis which included 22 studies to estimate the diagnostic accuracy of IFN-γ for pleural TB, noted sensitivity and specificity of 89% and 97%, respectively (58), while other series have described lower sensitivities (59). More recently, IFN-γ was compared to ADA in a TB-endemic setting and showed a significantly greater sensitivity than ADA (IFN-γ cut-off: 107.7 pg/mL) (60). Thus, it appears that in a high burden TB setting, IFN-γ may have a similar potential utility to the current use of ADA. However, the test is not yet widely available in clinical practice and important information is not yet available regarding false positives and negatives situations, as well as its utility in low TB burden settings, thus preventing definitive recommendations for its use.

NAA techniques for evaluation of TB pleuritis in HIV-negative patients appear to have high specificity but relatively low sensitivity. In a meta-analysis of HIV-negative patients, NAA tests had relatively low sensitivity (62%) but high specificity (98%) for diagnosing TB (61). The relatively high sensitivity of the Xpert MTB/RIF NAA assay contrasts with the sensitivity and specificity of 25% and 100%, respectively, reported in a series of 20 cases of confirmed TB from a region with high TB prevalence (62). More recently the Xpert assay was tested in a high prevalence HIV/TB setting and the sensitivity and specificity of Xpert MTB/RIF test were 28.7% and 96.6%, respectively, while the respective positive and negative predictive values were 96.1% and 31.1% (63). Xpert MTB/RIF test on pleural fluid does not accurately diagnose pleural TB and therefore cannot be used as an initial evaluation test in patients with suspected pleural TB.

Lysozyme is an enzyme found in the cytoplasmic granules of neutrophils which hydrolyses bacterial cell walls. Pleural fluid lysozyme concentrations are >15 mg/dL in 80% of cases of pleural TB (64,65), with highest concentrations found in empyemas due to both tuberculous and non-tuberculous bacteria (65). However, lysozyme is not specific for infection and concentrations may also be elevated in MPE (64). The pleural fluid: serum lysozyme ratio may be more useful than the absolute value of lysozyme. A ratio >1.2 has been reported to diagnose empyema with a 100% sensitivity for TB pleuritis and 95% specificity (65). However, in a separate study of 276 pleural effusions of heterogeneous aetiology, a threshold ratio of 1.1 was associated with a sensitivity of only 67% with specificity of 90% (64), thus casting doubt on its utility.

Additional biomarkers used in differentiating MPE from TB pleuritis are simultaneous measurements of pleural DcR3 and TNF-sR1 (66), while a further study assessed the specificity and accuracy of combinations of TNF- and ADA2 (67). Other novel biomarkers that may in the future, aid diagnosis of TB pleuritis include: hyaluronic acid, neopterin, leptin and fibronectin concentration in pleural fluid, although there is currently limited data, with variable sensitivities and specificities being reported (68). Urinary lipoarabinomannan ELISA has recently been evaluated for the diagnosis of TB in HIV-infected patients with paucibacillary disease and may also be useful in the diagnosis of pleural TB (69).

Pleural biopsy

The presence of caseating granulomas containing acid-fast bacilli on histological examination of the pleural surface is diagnostic of TB pleuritis (9). The demonstration of acid-fast bacilli is not an absolute requirement; the presence of caseating granulomas in high burden settings is considered adequate (18). Pleural tissue can be harvested either by means of closed pleural biopsies, thoracoscopy or open surgical biopsies (34). Access to thoracoscopy and open surgical biopsies is limited in many parts of the world where TB is endemic and, therefore, if pleural fluid analysis proves inconclusive, closed biopsy is the preferred next investigation. Ultrasound-guided biopsy techniques have gained popularity amongst pulmonary physicians and are becoming the standard of care for obtaining pleural tissue in patients with suspected TB pleuritis. Medical thoracoscopy is reserved for the small number of cases where closed pleural biopsies fail to provide a diagnosis (18,34). Ultrasound-guided pleural biopsy has a diagnostic yield of
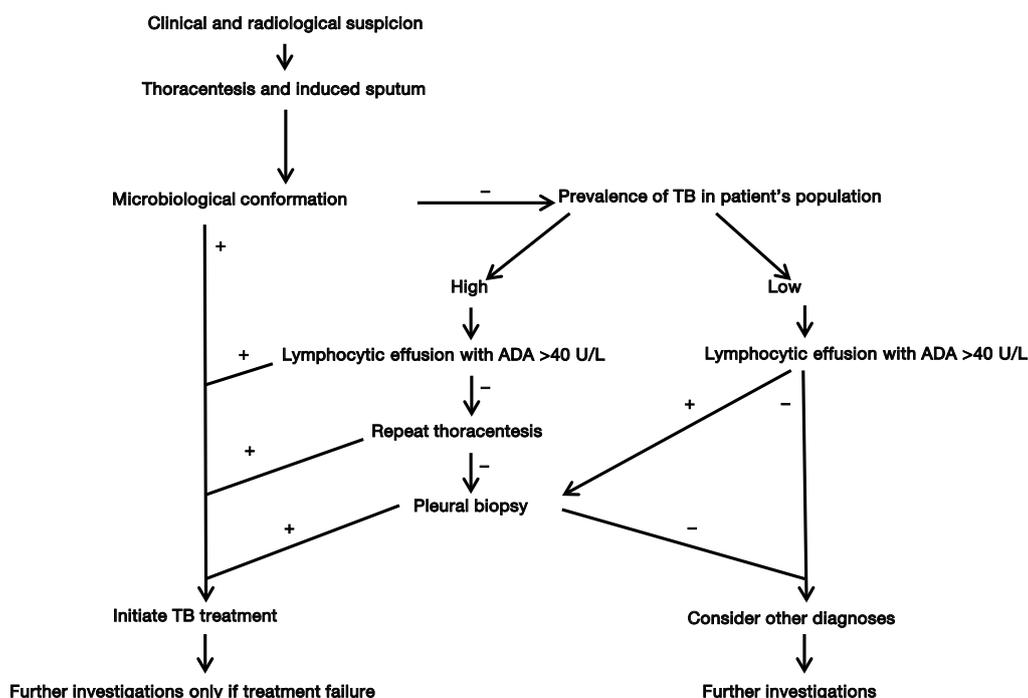
Figure 4 A suggested algorithm for the diagnostic evaluation of a patient who presents with a clinical and radiological suspicion of pleural TB. For the purposes of this approach, a high prevalence of TB is considered to be ≥125 per 100,000 population, whereas a low prevalence is <125 per 100,000. See text for detail on choice of biopsy technique (pleuroscopy *vs.* closed pleural biopsy). TB, tuberculosis.

up to 90% for pleural TB, which is not surprising given the diffuse nature of the disease (22).

Some centres prefer to use the Tru-Cut needle biopsies over the more conventional Abrams needle. Current evidence, however, still favours the Abrams needle as demonstrated by one study which found an overall diagnostic yield of 81.8% for the Abrams needle compared to 65% for the Tru-cut needle (35).

Because of sampling error, sensitivity generally increases with the number of biopsies taken, and biopsies taken during medical thoracoscopy have previously been found to have a diagnostic sensitivity of 100% (34). With medical thoracoscopy direct visualisation of the diseased pleura is possible, using either a rigid or a flexible endoscope, which guides the operator to the most appropriate biopsy site. Due to the reported high yield and less invasive nature of thoracoscopy, open surgical biopsies are seldom required.

Practical diagnostic approach

A practical suggested diagnostic approach, based on pre-

test probability, is presented in *Figure 4*. If the nucleated cell count is lymphocytic predominant with a high ADA (>40 U/L), and the background TB prevalence is high, it is prudent to initiate TB therapy. However, in a low prevalence population further confirmation is required by obtaining pleural biopsies for both histology and culture. Thoracoscopy has a superior diagnostic yield for both pleural malignancy and TB, and is therefore considered by many to be the investigation of choice in exudative pleural effusions where a thoracentesis was non-diagnostic. Pleural fluid findings are known to evolve from early neutrophil to lymphocytic predominance in TB effusions, and the value of repeat thoracentesis has been shown to significantly increase the diagnostic yield. In fact, we have shown that 77.8% of cases of confirmed pleural TB could be diagnosed on a second pleural aspiration in patients who previously had at least one non-diagnostic thoracentesis. In a high burden and resource constrained setting it may therefore be appropriate to repeat ultrasound guided thoracentesis before proceeding to pleural biopsy (70). An image-assisted second thoracentesis combined with an image-assisted

pleural biopsy with either an Abrams needle or cutting needle (depending on the clinical setting and imagery) may be an acceptable alternative to thoracoscopy, particularly when the probability of TB pleural effusion is high.

Treatment

The medical treatment for TB pleural effusion is the same as for pulmonary TB, and is consistent with the theory that the majority of pleural TB cases develop from pulmonary disease. The expected resolution of TB pleural effusion is variable, and assuming appropriate therapy, fever usually resolves within 2 weeks with reabsorption of the pleural fluid within 6 weeks. Naturally this will depend on the burden of disease in the individual, and size of the effusion and resorption may take up to 2-4 months.

The current evidence on the role of surgical intervention is limited and difficult to interpret, and intercostal drainage is traditionally not offered to patients unless severe dyspnoea is present (71,72). A recent study by Bhuniya *et al.* (73) investigated the use of early pleural drainage (using pleural manometry) in addition to standard anti-TB therapy, compared to standard therapy alone; and demonstrated significant differences after 6 months in lung function. The drainage group had a forced expiratory volume in the first second (FEV_1) of 87.6% as compared to the control group of 84.9% (P=0.02), with forced vital capacity (FVC) of 84.5% and 83.3% (P<0.01), respectively. The long term clinical relevance of these small differences in lung function is not known. However, these authors did report a lower incidence of residual pleural thickening in drained patients and also commented that patients with therapeutic thoracentesis experienced immediate relief from dyspnoea after drainage. Earlier studies reported that residual pleural thickening ≥10 mm can cause significant clinical symptoms in patients with TB pleural effusion, with reported incidences varying from 26% to 50.4% (25,26,73,74). In unpublished data, we found that patients with confirmed TB pleural effusions, randomised to therapeutic pleural drainage, showed significantly superior improvements in several lung function parameters after 3 and 6 months follow-up, despite complete drainage being achieved in less than half of all patients.

In selected patients, administration of corticosteroids can shorten the duration of fever and time to fluid resorption, although the risks and benefits of corticosteroids in this setting have not been well defined (75,76). Currently data is insufficient to support routine adjunctive use of corticosteroids for TB pleuritis (77).

Conclusions

On a global scale, TB remains one of the most frequent causes of pleural effusions. Our understanding of the pathogenesis of the disease has evolved and what was once thought to be an effusion as a result of a pure delayed hypersensitivity reaction is now believed to be the consequence of direct infection of the pleural space with a resultant lymphocyte driven immunological response. Pulmonary involvement is more common than previously believed and induced sputum, which is grossly underutilised, can be diagnostic in approximately 50%. The gold standard for the diagnosis of tuberculous pleuritis remains the detection of *M. tuberculosis* in pleural fluid or pleural biopsy specimens, either by microscopy and/or culture, or the histological demonstration of caseating granulomas in the pleura along with AFB. In high burden settings, however, the diagnosis is frequently inferred in patients who presents with a lymphocytic predominant exudate with a high ADA level, which is a valuable adjunct in the diagnostic evaluation. ADA is generally readily accessible, and together with lymphocyte predominance justifies treatment initiation in patients with a high pre-test probability. However, false-negative and false-positive results remain problematic. When adding closed pleural biopsy to ADA and lymphocyte count, diagnostic accuracy approaches that of thoracoscopy. The role of other biomarkers is less well described. Unstimulated pleural fluid IFN-γ or other newer assays, might lead to greater diagnostic accuracy, but further studies are required. Early pleural drainage may have a role in selected cases, but more research is required to validate its use.

Acknowledgements

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