

REVIEW ARTICLE

Tuberculous Pleural Effusion: An Update

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ABSTRACT

Pleural Tuberculosis (PTB) is a common manifestation of extra pulmonary tuberculosis (EPTB) and is a frequent cause of pleural effusion in high burden countries. Tuberculous pleural effusion (TPE) occurs in up to 25% of tuberculosis (TB) patients. TPE usually presents with fever, cough and pleuritic chest pain. The pleural fluid is an exudate that usually has predominantly lymphocytes. Owing to the paucibacillary nature of the pleural fluid, the diagnosis of TPE is a challenge. The definitive diagnosis of TPE is currently made by demonstrating the presence of tubercle bacilli in specimens such as pleural fluid and/pleural biopsies, or by histological examination of pleural tissue for granulomas. Pleural fluid cultures are positive for *Mycobacterium tuberculosis* in less than 40% and smears are virtually always negative. The one way to establish the diagnosis of TPE in a patient with a lymphocytic pleural effusion is to generally demonstrate a pleural fluid adenosine deaminase level above 40 U/L. In the last few years, there have been significant technological advances in the field of diagnosis of TB and MDR TB. The most exciting among them are the nucleic acid amplification tests (NAATs) for the diagnosis of TB. The use of NAATS for diagnosis of TPE has currently very limited utility. The chemotherapy for TPE is the same as that for pulmonary tuberculosis.

Key words: pleural effusion, adenosine deaminase, tuberculous effusion, gamma interferon, pleural biopsy.

INTRODUCTION:

Tuberculosis (TB) is one of the leading infectious causes of morbidity and mortality worldwide with estimated eight million new cases annually¹. Pleural TB is a common extrapulmonary manifestation of tuberculosis. Due to delayed type hypersensitivity reaction with alterations in permeability of pleural microvessels, pleural TB patients commonly develop effusion in the pleural cavity². In countries with high TB burden, it is recommended that TB should be excluded as a causative agent in patients with lymphocyte predominant exudative pleural effusion³.

Pakistan is ranked fifth among high TB burden countries with a significant proportion of pleural TB cases¹. Diagnosis and management of tuberculous pleural effusion (TPE) is challenging in the country due to poor sensitivity of current diagnostic method and increasing drug resistance. This review will highlight the current concept in epidemiology, pathogenesis, clinical manifestations laboratory diagnosis and management of TPE.

EPIDEMIOLOGY:

It has been reported that in around 25% of patients the TB will manifest itself with involvement of either pleura or lymph node⁴. In some areas it has been reported as the most common form of extrapulmonary TB⁵. Development of pleural effusion in such patient varies geographically and depends of the burden of TB in a particular setting^{6,7}. HIV co-infection aggravates this involvement with TB as a cause of pleural effusion in 86% of the cases in a series from Rwanda⁸. Pleural involvement in TB patient is higher in developing countries constituting 30% cases as compared to European countries which accounts for 3-5% cases^{9,10}. After pneumonia and malignancy, TB is considered to be the third common cause of massive pleural effusion¹¹.

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PATHOGENESIS:

The initial event resulting in TPE is rupture of subpleural caseous foci into the pleural space. Mycobacterial antigens are released resulting in delayed hypersensitivity reaction mediated by CD4 lymphocytes^{2, 10}. This hypersensitivity could occur in primary or reactivation TB (commoner in adults especially in developing countries) and is independent of presence of viable mycobacteria. An intense inflammatory response mediated initially by neutrophils and macrophages and later by T lymphocytes is initiated resulting in increased permeability of pleural microvessels that in turn leads to development of TPE. Lymphatic obstruction leads to decrease pleural fluid clearance which in turn causes accumulation of pleural fluid^{2,12}.

CLINICAL MANIFESTATION:

TPE can present as an acute, sub-acute or chronic illness. It is more common in young patients compared to parenchymal TB. Around 75% cases present as pleuritic chest pain and around 70% have nonproductive cough^{2, 4, 10}. Fever is one of the manifestations but around 15% of patients could be afebrile. TPE can present as a small to moderate size unilateral effusion and in case of large effusion patient will present with shortness of breath^{2, 4, 10}. Co-existing parenchymal disease is seen on chest radiograph in approximately 20% with TB pleural effusion and this proportion increases up to 80% when CT chest is performed¹³.

DIAGNOSIS:

Pleural Fluid Examination:

Pleural fluid analysis assists in presumptive diagnosis of tuberculosis is depending on the prevalence of TB^{10, 12, 14}. TPE in almost all cases is exudative with a protein concentration of greater than 5 g/dL. The predominant cell type is lymphocyte in majority of patients ranging from 50-90%. In initial stages of illness neutrophils could be found in majority and presence of exudate with neutrophilic predominance should not rule out TPE diagnosis¹⁵. These neutrophils are however replaced by lymphocytes within 1-2 week¹⁵. Although not very specific but a low glucose concentration and high lactic acid dehydrogenase also points towards the possibility of TPE. On the other hand presence of more than 10% of eosinophils or more than 5% of mesothelial cells make the diagnosis of TPE less likely^{10, 12, 14}. A recent study evaluating the role of pleural fluid analysis alone in 548 samples for the diagnosis TPE reported that in one third of TPE cases pleural fluid analysis alone was diagnostic¹⁶. They also reported a high probability in nearly 60% of the cases¹⁶.

Microbiological Diagnosis:

The definitive diagnosis of TPE is currently made by demonstrating the presence of tubercle bacilli in specimens such as pleural fluid and/pleural biopsies, or by histological examination of pleural tissue for granulomas^{2, 4}. However the extended time periods required for isolating and identifying MTB from samples of pleural effusion and the limited sensitivity of the techniques employed have hampered the diagnosis of TPE^{2, 4, 17}.

Pleural fluid Microscopy:

Pleural fluid has been reported to be a poor source of mycobacteria. Direct examination of pleural fluids by Ziehl-Neelsen staining requires bacillary densities of 10,000/ml, whereas for isolation by culture 10-100 viable bacilli are needed^{17, 18}. Microscopy in TPE cases is positive in less than 10% of the cases in immunocompetent patients with higher positivity in tuberculous empyema cases^{2, 18, 19}. Sensitivity of smears is significantly higher in HIV positive individuals⁷.

CULTURE:

Sputum smear and culture:

Sputum cultures for the diagnosis of TPE, although useful but are usually not requested². Yield of spontaneous sputum culture ranges from 0-30% with higher positivity in patients with concomitant lung parenchymal involvement¹⁸. Culture of induced sputum in a case of TPE has also been advocated. A higher culture yield of 52% in induced sputum versus 12% in pleural fluid culture has been reported²⁰. Another study showed sputum positivity in around 22.2% with TB pleural effusion highlighting the value of sputum culture in TPE cases²¹.

Pleural Fluid culture:

Cultures of pleural fluid are positive in less than 60% of patients with TPE^{2, 18}. Conventional culture is also slow with a mean time to positivity with the BACTEC system of around 3.5 weeks with the Lowenstein–Jensen medium of 4.7 weeks^{2, 4}.

Closed Pleural Biopsy:

Several investigators have reported that pleural biopsies are the most reliable for diagnosis of TPE provided the appropriate site is available for examination^{2, 4}. In one study of 248 patients with tuberculous pleuritic 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 (25.8%) and the culture of the biopsy tissue was positive in 140 (56%)¹⁹. However, the invasiveness of the procedure, inability to obtain characteristic pleural tissue leading to false negative results in 15-20% cases and the accompanied complications limits the utility of this technique².

Detection of inflammatory/immune biomarkers:

Due to the limitations of the conventional methods newer rapid tests based on detection of inflammatory and immune marker have been evaluated. Several nonspecific and immune response markers have been evaluated for the diagnosis of TPE. This includes measurements of Adenosine deaminase (ADA), Neopterin, Leptin, Lysozyme, Fibronectin, Interferon gamma (IFN- γ) and IL-2¹⁷. However of these ADA and IFN- γ will be discussed in detail due to their best and consistent role in TPE diagnosis. Recently use of T cell based IFN- γ release assays (IGRAs) have also been shown to be effective in TPE diagnosis in specific settings. In contrast antibody detection assays have not been endorsed so far for the TPE diagnosis due to their poor and variable sensitivities.

Adenosine Deaminase:

Estimation of adenosine deaminase (ADA) in pleural fluid has been used widely as biochemical markers in the diagnosis of TB pleural effusion^{2, 17, 22-24}. ADA is a non-specific biomarker of inflammation that is released by activated lymphocytes, macrophages and neutrophils. A recent meta-analysis of 63 studies including 2796 patients with TPE and 5297 with non-tuberculous effusion reported a sensitivity and specificity of 92% and 90% respectively of ADA in the diagnosis of pleural TB with a diagnostic odds ratio of 110.08²³. They also that in high TB prevalence setting a positive ADA test will provide a 99% post- test probability of TB. The most widely accepted cut-off value for pleural fluid ADA is 40 U/L². Castro *et al.* measured the pleural fluid ADA levels in 410 lymphocytic non-tuberculous pleural fluids and found that the ADA was above 40 IU/L in only seven (1.7%) patients²⁴. It is reported that the likelihood of TB increases with the level, the greater is the level the greater is the chance of the patient having TB². However these biomarkers are indicative of an inflammatory process in the pleural cavity and do not define or identify the etiological agent. Studies have compared the level of ADA², an isoenzyme of ADA found in monocytes to total ADA and have found it to be an efficient and better marker than total ADA¹⁷. However it should be emphasized that the results of ADA test should be related to clinical context to make an efficient diagnosis.

Gamma Interferon:

Several studies have reported IFN- γ as a sensitive and specific marker for diagnosing TPE¹⁷. It is a cytokine released by activated CD4 T lymphocytes. A recent review analyzed the diagnostic performance of IFN- γ in TPE and confirms the high diagnostic utility of this test²⁵. Another meta-analysis evaluating 22 studies reported a sensitivity and specificity of 89% and 97% respectively²⁶. Combined utility of ADA and IFN- γ had a maximum joint sensitivity and specificity of 93% for ADA and 96% for IFN- γ . Although some studies have reported IFN- γ was to be more useful than ADA, IFN- γ is not preferred in a resource constraints setting due to high cost and complexity.

Gamma interferon release assays:

Recently the role of T cell based IFN- γ release assays (IGRAs) have also been evaluated for the diagnosis of TPE¹⁷. This test is designed to detect latent TB and is not yet endorsed by the WHO for the diagnosis of active TB. A meta-analysis was conducted to evaluate utility of IGRAs for the diagnosis of active TB²⁷. In this meta-analysis studies reporting effectiveness of IGRA for diagnosis of TPE were also included. The pooled sensitivity and specificity of IGRA in the five studies that were included was 88% and 82% respectively. However these results were variable with the type of IGRA used and higher sensitivity and specificity was seen with T-SPOT.TB than QFT-G-IT. The authors concluded that the diagnostic accuracy of IGRAs was not sufficient to use this test to exclude TB²⁷. They also stated that although a higher sensitivity and specificity of IGRAs was seen in fluids than blood further studies are required to recommend its widespread use for the diagnosis of TPE. Other authors have also suggested using ADA rather than IGRAs for TPE diagnosis due to its low cost and wide availability²⁸.

Due to the limitation of the above discussed methods scoring systems based on both laboratory and clinical have also been developed. These systems have been reported to be highly relevant and user friendly in high TB burden resource limited settings.

MOLECULAR DIAGNOSIS:

Nucleic acid amplification tests:

In the last few years, there have been significant technological advances in the field of diagnosis of TB and MDR TB. The most exciting among them are the Nucleic acid amplification tests (NAATs) for the diagnosis of

TB. The two tests which have generated maximum interest are GeneXpert system (Xpert MTB/RIF) and Line Probe Assays (LPA).

A recent study has evaluated Xpert MTB/RIF for pleural TB diagnosis and reported a sensitivity and specificity of 63% and 100% respectively²⁹. Another study have evaluated 20 cases of confirmed TPE and found it to be 25% sensitive and 100% specific³⁰. The authors suggested that the sensitivity of this assay could be increased by optimization of sample collection, transport and processing. A recent study evaluating Xpert MTB/RIF for the diagnosis of TPE reported a sensitivity of 16% and specificity of 100%. The sensitivity of Xpert MTB/RIF performed on pleural tissue in the same study was 0% as the assay missed all culture positive cases³¹. In contrast to other body fluids and tissues, the limited sensitivity of Xpert MTB/RIF in pleural fluid and tissue could be explained by PCR inhibitors or low burden to TB bacilli in these specimens. Therefore use of Xpert MTB/RIF for diagnosis of TPE has currently very limited utility.

Although the LPA were developed about 15 years ago, they became a popular diagnostic method recently, after WHO recommended a new policy of using line probe assays for rapid screening of patients at risk of MDR TB in 2008³². The two commercially available line probe assays include INNO-LiPA Rif.TB (Innogenetics, Ghent, Belgium) targeting *rpoB* gene and GenoType MTBDRplus (Hain Lifescience GmbH, Nehren, Germany)

targeting *rpoB*, *katG* and *inhA* genes in both culture isolates and clinical samples. MTBDR*plus* assay permits the molecular genetic identification of *M. tuberculosis* complex and its resistance to rifampicin (Rif) and INH from culture isolates and clinical specimens directly^{33, 34}. Although widely used for the diagnosis of pulmonary TB, with the utility of these tests in other extrapulmonary TB specimens³⁵, MTBDR*plus* have not been evaluated for diagnosis of TPE in clinical setting.

Pleuroscopy:

It is an invasive technique which requires expertise and should be done in patients in whom diagnosis is unclear despite extensive workup. Adhesions and tubercles on parietal pleura can be seen via pleuroscopy and biopsy of the lesion is possible under direct vision³⁶. Pleuroscopy has a diagnostic accuracy up to 100% with complication rates as low as 2-5%³⁷.

TREATMENT:

It is expected that around 50% of untreated patient with TPE will develop active TB². Therefore the goal of treatment of TPE should be to treat the infection, prevent the subsequent development of active TB, prevent the emergence of drug resistance, to relieve the symptoms of the patient, and to prevent the development of complication like fibrothorax.

Treatment is essentially same as of pulmonary TB. Initial phase of the treatment consists of four drugs that include isoniazid, rifampicin, pyrazinamide and ethambutol. The continuation phase includes four month treatment with isoniazid and rifampicin. Drug susceptibility testing should be done and treatment should be modified later according to the susceptibility. With effective therapy the resolution of fever generally occurs in two weeks and pleural fluid is resorbed in six weeks. A paradoxical enlargement in the size of pleural effusion may be seen in the early phase of treatment in 10-15% of patients. Complete resolution of pleural fluid after initiation of treatment can take 6-12 weeks³⁸.

Around 50% of the patients can have residual pleural thickening post treatment³⁹. The residual pleural thickening is more common if the pleural effusion is initially loculated, with a low pleural fluid glucose, a high pleural fluid LDH level and high pleural fluid cytokine levels^{40, 41}. Regular follow up and monitoring can help with the compliance and reduce the risk of drug resistance.

If the patient is more than mildly symptomatic, a therapeutic thoracentesis is recommended. Except for patients with large pleural effusion, complete drainage of pleural fluid does not affect short term or long term outcome and is not routinely recommended.

Role of steroid therapy has been controversial in TPE. A Cochrane review that evaluated the effectiveness of steroid in the management of TPE found no sufficient evidence of steroids⁴². A study performed on 190 patients showed no role of steroids in the management of TPE⁴³. In two controlled studies in which therapeutic thoracentesis were performed also failed to show any added benefits^{44, 45}. The administration of corticosteroids did not decrease the degree of residual pleural thickening^{44, 45}.

SUMMARY:

Pleural TB is a common extrapulmonary manifestation of tuberculosis. The possibility of TPE should be considered in every patient with an undiagnosed lymphocyte predominant exudative pleural effusion. The definitive diagnosis of TPE needs presence of tubercle bacilli in specimens such as pleural fluid and/pleural biopsies, or by histological examination of pleural tissue for granulomas. The presumptive diagnosis can be made with history suggestive of TB, presence of an exudative lymphocytic effusion and high adenosine deaminase level in pleural fluid. In the last few years, there have been significant advances in the Nucleic acid amplification tests for the diagnosis TB but the utility of NAATS for diagnosis of TPE has currently very limited. The chemotherapy for TPE is the same as that for pulmonary tuberculosis. The use of steroids is not recommended in the management of TPE.

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