

## Atypical Manifestations of Tuberculous Pleural Effusions

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### ABSTRACT

Typically, a tuberculous pleural effusion is submassive, unilateral, and has the appearance of being straw coloured, and a cellular content which is predominantly lymphocytic. Atypical stigmata do, however, have to be recognised, so as to mitigate the risk of diagnostic delay, the latter sometimes resulting in potentially avoidable deaths and risk of transmission of tuberculosis to close contacts.

### Introduction

In the United States of America, during the period 1993-2006, 19.8% of 42,793 patients in the National Tuberculosis Surveillance System database were documented as having Tuberculous Pleural Effusion (TPE) [1]. During that period pleural effusion was second only to lymph node involvement as an extrapulmonary manifestation of *M. tuberculosis* (MTB). Even in the context of Human Immune Deficiency Virus (HIV) infection, TPE is outranked only by tuberculous lymphadenopathy as an extrapulmonary manifestation of MTB infection [2]. Furthermore, on the basis of data compiled from 6 countries, among MTB patients co-infected with HIV, TPE is twice as prevalent as in HIV-negative subjects [3], arguably as a consequence of the fact that TPE becomes significantly ( $p=0.03$ ) more prevalent as the CD4 cell count falls [4].

TPE is typically a disease of adults, with a peak incidence in the 21-30 age group [5,6]. In the paediatric age group 39 patients with TPE were identified in a Spanish study enrolling 175 children aged <18 (including those aged <5) with intrathoracic MTB infection. The mean age (13.52) of those with TPE was significantly ( $p < 0.001$ ) higher than the mean age (6.97) of those who did not have this complication [7].

Thanks to Computerized Tomography (CT) imaging it is now recognised that TPE is typically associated with parenchymal lung disease [8]. In the latter prospective study of 106 TPE patients aged 16-89 parenchymal lung disease was identified by "simple" chest radiography and by CT, in 67% and in 86%, of patients, respectively [8]. Cavitary lung disease was documented in 19% of the 91 TPE subjects with CT-identifiable parenchymal disease [8]. A subsequent study has shown that, among patients with TPE, pleural fluid Adenosine Deaminase (ADA) levels are highest in the subgroup with CT documented cavitary parenchymal disease [9]. The implication of the latter

observation is that, in the event of a patient having a smear-negative pleural effusion concurrently with a smear-negative sputum, and in the event that the patient is too frail to have a pleural biopsy, the association of cavitary parenchymal disease (whether by chest radiography or by CT) and exudative pleural effusion with high (> 80 iu/L) ADA levels would be strong presumptive evidence of a tuberculous aetiology. CT also detects centrilobular lesions and areas of alveolar consolidation in patients with TPE, and the latter occur also when TPE is characterized by neutrophil predominance [10]. Conversely, however, parenchymal stigmata may, occasionally, be entirely absent on CT imaging of TPE, even in the presence of culture-positive sputum [8].

Notwithstanding all the above considerations, plain chest radiography, rather than CT, is the most accessible first line modality for generating some of the typical stigmata of TPE, namely, an effusion which is unilateral, and rarely occupies more than 2/3 of the hemithorax [11]. Typical characteristics of the effusion, itself, include a straw coloured appearance, and a cellular profile characterized by lymphocyte predominance, except during the first two weeks of its onset, when neutrophils may predominate [11].

Atypical radiographic features of TPE include pleural shadowing occupying the entire hemithorax, bilateral effusions, paradoxical worsening of the pleural effusion after initiation of antituberculous chemotherapy, hydropneumothorax, and absence of concurrent parenchymal disease on CT.

Atypical appearance of the aspirated pleural effusion includes "bloody" appearance, purulent appearance, and chylous or pseudochylous characteristics.

Atypical microscopic stigmata include neutrophil predominance in the presence of alveolar consolidation, thereby simulating parapneumonic effusion attributable to bacterial pneumonia.

Co-infection is another atypical feature. Co-pathogens which have been identified include gram positive diplococci, nocardiosis, and *Cryptococcus neoformans*, respectively.

Exceptionally, TPE can coexist with asbestos-related pleural disease, carcinomatosis, haematological malignancies, sarcoidosis and systemic lupus erythematosus, respectively, each of those disorders being independently capable of causing pleural effusion in their own right.

### Atypical Radiographic Stigmata

In one study the pleural effusion occupied the entire hemithorax in 8% of 113 patients with TPE [12]. In another study, among 254 patients with TPE, 19.5% had effusions which occupied > 2/3 of the hemithorax [4].

A bilateral distribution of the effusion may also be a feature of TPE, as in 10% of 167 patients evaluated in one study [5]. A paradoxical increase in the size of the effusion may also occasionally occur after commencement of antituberculous (ATT) chemotherapy. This was the case in a patient who initially presented with small bilateral effusions which were not "tappable". Fine needle aspiration of concurrent mediastinal lymphadenopathy yielded m tuberculosis on culture. Six weeks after commencing ATT chemotherapy the patient presented with a massive right-sided chylous pleural effusion [13].

Also paradoxically, a contralateral pleural effusion may appear for the first time after initiation of ATT chemotherapy [14]. In the latter example the contralateral effusion (left sided) developed while the initial pleural effusion (right-sided) was subsiding. Pleural biopsy on the left side showed granulomatous inflammation with caseation. Both effusions resolved completely when prednisolone was added to the ATT chemotherapy regime [14]. In another example of contralateral effusion during antituberculous chemotherapy the initial effusion was a left sided exudate with lymphocyte predominance, and an ADA content of 64 iu/L. Subsequently, the patient developed a right sided exudative effusion with neutrophil predominance and an ADA content of 21 iu/L. However, Gene Expert evaluation of the right sided effusion tested positive for a tuberculous aetiology [15,16]. Both effusions resolved during the course of ATT chemotherapy [15].

Bilateral effusions with discordant characteristics also occur outside the context of paradoxical response to ATT chemotherapy. In one such case, a 72 year old patient, the left sided effusion had a 92% lymphocyte content, and the right sided effusion a 90% neutrophil content, both effusions being culture-positive for *M. tuberculosis* [16].

Bilateral pleural effusions may also occur in miliary tuberculosis. In one patient, with eventually fatal miliary tuberculosis and bilateral pleural effusions, the left-side effusion was characterized by a total white cell count of 5720 cells/microlitre, with 95% neutrophils. At autopsy MTB was cultured from the pleural fluid, right and left lung cultures, and from sputum. There was no evidence of bronchopneumonia [17].

Hydropneumothorax may also be a feature of TPE. In one study, among 57 patients with hydropneumothorax prospectively evaluated in an Indian tertiary hospital, pleural fluid acid fast bacilli smear was positive in 8 patients, mycobacterial culture on Lowenstein-Jenson media generated growth in 5 patients, MGIT media generated growth in 10 patients. The remaining 22 patients were evaluated by CT. A final aetiological diagnosis of tuberculosis was reached in 40 patients [18]. However, even in the high tuberculosis prevalence context of Nigeria, hydropneumothorax had a prevalence of only 6% among the 167 TPE patients in that study [5].

Occasionally, a patient with TPE may have total absence of concurrent parenchymal lung disease even when evaluated by CT. This was the case in 2 out of 106 TPE patients, aged 16-89, prospectively evaluated by CT [8].

### Atypical Appearance of the Pleural Effusion

#### 1. Tuberculous pleural effusions which are “bloody” or “haemorrhagic”

In a prospective French study 11.5% of 52 TPE patients were characterised by pleural effusions which were “bloody” in appearance [19]. In a Nigerian study of 167 TPE patients 11.8% were identified as having a “haemorrhagic” pleural effusion [5]. The likelihood of mistaking a MTB-related bloody or haemorrhagic

effusion for neoplastic disease is high when the blood stained effusion is massive, as was initially the case in a 18 year old patient in whom the effusion eventually proved to be culture positive for MTB [20].

#### 2. Purulent tuberculous pleural effusions

A purulent appearance was noted in 7.8% of TPE patients in one study [5], and in 13.46% of 52 TPE patients in another study [19]. Tuberculous empyema is a subtype of purulent MTB-related effusion. According to an estimate made in 1995 this is a complication in approximately 1-4% of patients with pulmonary tuberculosis [21]. The diagnosis is suspected when, on CT, there is a thick calcific pleural rind and rib thickening surrounding loculated pleural fluid [22]. Occasionally, tuberculous empyema is massive, occupying the entire hemithorax, even when MTB is the sole pathogen [23].

#### 3. Chylous pleural effusions

In one study this was a feature in 2 out of 167s patient with TPE [5]. Chylous pleural effusions have a milky appearance and the content includes chylomicrons and triglycerides, the latter amounting to > 110 mg/100 ml [24]. Identification of chylothorax as well as pseudochylothorax can be optimized by routine centrifugation of all turbid pleural aspirates. When turbidity of pleural fluid is attributable either to chylothorax or to pseudochylothorax the supernate remains turbid even after centrifugation [24].

Chylothorax can be culture positive for MTB even in the absence of concurrent lymphadenopathy [25]. In other cases culture-positive chylothorax occurs in association with tuberculous lymphadenopathy, arguably as a result of erosion or compression of the thoracic duct by enlarged lymph nodes [26].

Sometimes, the precipitating cause of culture-positive chylothorax is the immune reconstitution syndrome following antiretroviral treatment [27].

Occasionally, chylothorax can coexist with tuberculous empyema, as was the case in a 67 year old patient in whom these two complications were attributable to rupture of a tuberculous spinal abscess in the T12/L1 region. Initially, the patient had a purulent pleural effusion which communicated with the paravertebral abscess through the diaphragm. The effusion contained

acid fast bacilli fully sensitive to antituberculous chemotherapy. Subsequent to repeated aspiration of the empyema the fluid turned milky, and further analysis revealed a triglyceride content > 110 mg/dl [28].

#### 4. Pseudochyolous pleural effusions

This is a milky pleural effusion with a cholesterol content of >250 mg/dl [24]. Numerous cholesterol crystals are identified on microscopic examination. A tuberculous aetiology was validated by a positive nucleic acid amplification test on the pleural fluid in a 72 year old woman who presented with a pseudochylothorax occupying > 2/3 of the right hemithorax [29]. The authors of a 1999 review reported two cases of their own, with tuberculosis as the underlying cause. They identified 95 additional tuberculosis-related cases in the medical literature [29]. Risk factors for tuberculosis-related pseudochylothorax included collapse therapy, and pleural effusion duration exceeding 5 years [30]. However, bacteriological validation of a tuberculous aetiology was achievable in only 13 of the 95 cases, either through pleural fluid culture, pleural biopsy culture, or sputum culture. In only two cases was a smear of the pleural fluid positive prior to culture [30]. However, in another analysis, 104 cases of pseudochylothorax were culled from a systematic review of 62 studies. *M. tuberculosis* was cultured from the pleural effusion in 34.1% of those cases [31].

#### The Association of Alveolar Consolidation with a Neutrophil Predominant TPE

In a retrospective review of 354 adult TPE patients in a university hospital in Taiwan (from January 2000 to April 2007) 39(11%) of the patients were identified who had a neutrophil predominance in the pleural effusion [32]. Among those were 27 subjects in whom a neutrophil-predominant TPE was associated with alveolar consolidation. This subset comprised 7.6% of the entire group of 354 TPE subjects. When a neutrophil-predominant TPE is documented in a patient with alveolar consolidation [32] there is a risk of mistaken diagnosis of parapneumonic effusion attributable to bacterial pneumonia [32]. A consequence of mistaken diagnosis is futile antibiotic therapy,

delayed diagnosis of tuberculous aetiology, sometimes with fatal consequences [32]. In this context ADA levels do not generate diagnostic clarity, given the fact that ADA levels >40 iu/L occur both in neutrophil predominant effusions which are TPE-related and in those which are attributable to bacterial pneumonia [10]. Timely identification of a tuberculous aetiology should be sought from evaluation of the pleural biopsy specimen by Polymerase Chain Reaction (PCR) using the Xpert MTB/RIF assay. When mycobacterial culture from a pleural biopsy specimen is used as a reference standard for sensitivity and specificity calculations the Xpert MTB/RIF assay generates a sensitivity of 85.5% and a specificity of 97.2% for identifying a tuberculous aetiology for pleural effusion [33].

#### Dual Pathology in TPE

Co-infection with other pathogens may occur in some cases of TPE. Co-pathogens include gram positive diplococci [34], nocardia species [35], and *Cryptococcus neoformans* [36]. The latter case was characterized by positive sputum culture for mycobacterium tuberculosis, signifying parenchymal tuberculosis, adenosine deaminase content of 101 iu/L in the pleural fluid, and a growth of *C. neoformans* in the pleural fluid, signifying pleural cryptococcosis [36]. Conversely, TPE which is characterized by MTB culture positivity in the pleural fluid, and MTB culture-positive sputum, can coexist with cryptococcal lung disease, the latter a risk factor for subsequent cryptococcal meningitis [37]. Diagnostic confusion is compounded by the fact that cryptococcal pleural effusion simulates TPE by being characterized by lymphocyte predominance as well as by high ADA levels [38].

Coexistence of TPE and asbestos-related pleural disease was documented in a patient who had pleural plaques compatible with asbestos-related disease, and *M. tuberculosis* on culture of the pleural fluid [39].

TPE may also coexist either with carcinomatosis or haematological malignancy. In one study, among 450 consecutive patients with TPE, there were 20 who had either concurrent carcinomatosis or concurrent

haematological malignancy. In eighteen m tuberculosis infection was validated by culture-positive pleural fluid, and in two instances, by histopathological criteria [40]. In another report a blood stained effusion was documented in a 54 year old woman with a strongly positive tuberculin test.. The effusion resolved after a therapeutic trial of antituberculous chemotherapy notwithstanding the fact that subsequent pleural biopsy showed squamous cell carcinoma from an unknown primary [41]. Biopsy-proven tuberculous pleural effusion can also coexist with biopsy-proven sarcoidosis [42]. In the latter context diagnostic confusion would be attributable to the fact that sarcoidosis can cause pleural effusion in its own right [42]. The same is true when tuberculous pleural effusion occurs in a patient with systemic lupus erythematosus [43].

### Non Diagnostic Adenosine Deaminase Levels

The occasionally occur in patients with proven tuberculous pleural effusions [16,44]. In one instance of a patient with bilateral pleural effusion the right sided pleural effusion had a neutrophil predominance and was characterized by a serum ADA level of 21 iu/l notwithstanding the fact that the pleural effusion tested positive for *M. tuberculosis* when evaluated by PCR [16]. In another example the pleural effusion had an ADA level of 8 iu/l notwithstanding the fact that “PCR report returned as positive”. The effusion showed marked reduction after commencement of antituberculous chemotherapy [44].

### Conclusions

TPE is a potentially life-threatening disease [17,32], and TPE patients can transmit MTB to their close contacts [45]. For those reasons even its atypical manifestations deserve to be highlighted.

### Highlights

(i) Although typically unilateral, submassive, and characterize by a clear, straw coloured appearance, and lymphocyte predominance, tuberculous pleural effusion can, occasionally, be massive, and bilateral, with an appearance best described as bloody, in some instances, purulent, in other instances, and , in rare instances, chylous and even pseudo-chylous.

(ii) An erroneous presumptive diagnosis of carcinomatosis might be made if the effusion is both massive and bloody, and an erroneous diagnosis of parapneumonic pleural effusion (attributable to bacterial pneumonia) might be made if a neutrophil predominant tuberculous pleural effusion is documented in a patient with alveolar consolidation. Timely recourse to PCR may potentially avert such misdiagnosis.

(iii) Bilateral pleural effusions may be a feature of untreated tuberculosis, including miliary tuberculosis. A contralateral pleural effusion cans also a rise de novo, during the course of antituberculous chemotherapy. In both contexts there may, sometimes, be discordance in the cellular content of the two coexisting pleural effusions.

(iv) In the presence of hilar lymphadenopathy, and sometimes even in its absence, chylous pleural effusion may be a manifestation of culture-positive tuberculosis. It may also be a manifestation of HIV-related immune reconstitution inflammatory syndrome.

(v) Pseudo-chylothorax may be an underrecognised manifestation of tuberculous pleurisy. Its recognition would be enhanced by routine centrifugation of all turbid pleural aspirates.

(vi) In the presence of pleural effusion (including empyema) m tuberculosis can coexist with pathogens such as gram positive diplococci, nocardia species. Pleural effusion attributable to *Cryptococcus neoformans* can coexist with sputum-positive pulmonary tuberculosis. Conversely, culture-positive TPE can coexist with pulmonary cryptococcosis. TPE can also coexist with carcinomatosis, and haematological malignancies, respectively.

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