

Pleural tuberculosis

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ABSTRACT: *Pleural tuberculosis. B. Chakrabarti, P.D.O. Davies.*

Pleural effusions in tuberculosis are commonly seen in young adults as an immunological phenomenon occurring soon after primary infection. However, the epidemiology and demographics of tuberculous pleurisy are changing due to the impact of HIV co-infection and the increasing number of pleural effusions seen as part of re-activation disease. Pleural biopsy for histology and culture is the mainstay of diagnosis with closed needle biopsy ade-

quate in the majority of cases. Techniques such as PCR of biopsy specimens and the role of pleural fluid ADA are still being evaluated as a diagnostic aid. Tuberculous empyema is less commonly seen in the western world and the diagnostic yield from pleural fluid here is greater than in "primary" effusions. Treatment with appropriate anti-tuberculous chemotherapy is generally successful though there is currently insufficient evidence to recommend the routine use of corticosteroids in this condition.

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Epidemiology

The incidence of pleural tuberculosis is difficult to determine with precision. In the United Kingdom, pleural involvement is seen in less than 10% of cases of infection with *Mycobacterium Tuberculosis* [1-3]. In 1993, a notification survey of England & Wales reported the incidence of pleural involvement at 9% (153 of 1699 cases) [1]. This compares to an incidence of 6% seen in surveys performed in 1983 and 1979 covering the same area [2, 3]. Pleural disease is seen more frequently in ethnic minorities with active tuberculosis living in the western world. In the 1993 England & Wales survey, a higher proportion of tuberculosis cases exhibiting pleural involvement were seen in the Indian subcontinent ethnic group compared to white Caucasian individuals (11% and 7.1% respective-

ly) [1]. The same trend was seen in the 1983 survey where the incidence of pleural involvement was 8% in the Indian subcontinent group compared with 5% in white Caucasians [2]. In a large Turkish study involving 5480 cases of tuberculosis, pleural effusions were noted in 6.3% and pneumothoraces in 1.5% [4]. However, the epidemiology of pleural tuberculosis may be quite different in other countries, particularly in Africa, due to the impact of HIV infection (see table 1). One study from Tanzania reported 38% of all tuberculosis cases exhibiting pleural involvement [5].

Pleural tuberculosis is most commonly seen in adolescents and young adults as opposed to children and the elderly. In the 1983 UK survey, only 5 children out of 119 (4.2%) were documented to have pleural involvement [2]. Patiala describes that the incidence of pleural TB was highest at the

Table 1. - Pleural involvement in the epidemiology of tuberculosis

	Geographical area	Total number of tuberculosis cases	Number exhibiting pleural involvement	% of cases exhibiting pleural involvement
National survey 1993 [1]	England & Wales, United Kingdom	1699	153	9
National survey 1983 [2]	England & Wales, United Kingdom	2001	129	6.4
National survey 1979 [3]	England & Wales, United Kingdom	1267	86	6.8
Seibert et al [9]	Alabama, USA	1738	70	4
Moudgil et al [10]	Scotland, United Kingdom	1134	82	7.2
Akotgu et al [4]	Turkey	5480	343	6.3
Mlika-Cabanne et al [5]	Tanzania	146	56	38

age of 18 in a large Finnish study and in a detailed Romanian study; the peak age of incidence of pleural tuberculosis was reported in the 20-24 years group at 19.1/100,000 in 1990 [6, 7]. However, other studies appear to show that the mean age of pleural tuberculosis is increasing which may reflect the increasing incidence of post-primary or "re-activation" disease and the burden of HIV seen in clinical practice. Epstein et al reported a mean age incidence of 56 in a series of 26 patients with pleural tuberculosis and the mean age in a series of 70 patients in Alabama, USA (Seibert) was 47 years [8, 9].

Pathophysiology

Tuberculous pleural effusions usually occur after a so called latent period of 3-6 months following the initial infection as a result of rupture of the Ghon focus into the pleural cavity. The aetiology of such "primary" tuberculous effusions lie in a delayed hypersensitivity reaction to a few bacilli entering the pleural space; an immunological phenomenon rather than one of direct infection of the pleural space. This would explain a period of latency from the time of initial infection, the low yield of pleural fluid acid fast smear analysis in this condition and often the lack of positive pleural fluid cultures. Exudation of plasma proteins occurs with the accumulation of CD4+ cells and the release of inflammatory mediators such as Interferon Gamma (IFN- γ).

Tuberculous effusions can also occur as a result of direct spread of bacilli from cavitory lung lesions, the bloodstream and the lymphatic system in post-primary disease i.e. one of direct infection of the pleural space rather than a primary immunological phenomenon. Traditionally, this was seen less commonly than in primary disease as a so-called "re-activation" phenomenon with the presence of parenchymal infiltrates or cavities in the upper lobes used as a means of distinction from primary disease [12]. However, recent studies appear to suggest that "re-activation" disease is becoming a more frequent presentation of tuberculous pleurisy. A study of tuberculous pleural effusions in Scotland reported that "re-activation" disease was in fact more commonly seen than primary disease [10]. Here, larger numbers of acid-fast bacilli are secreted into the pleural cavity compared to primary tuberculous effusions. Such chronic active infection may lead to the development of a tuberculous empyema as described later. Rupture of a parenchymal cavity into the pleural space can also result in the development of a bronchopleural fistula and pyo-pneumothorax.

Clinical features and sequelae

The clinical features of primary tuberculous effusions include dyspnoea, fever, malaise and pleuritic chest pain though cases may also be oligo or asymptomatic. In a substantial number of cases, the presentation may be acute with the aforementioned symptoms presenting over short duration particular-

ly in immunocompetent individuals [11]. In post-primary "re-activation" disease as well as in immunocompromised individuals, symptoms may be present for longer periods. In one study the duration of illness was 14 days in primary disease compared with 60 days in secondary cases [12]. Such effusions may be of significant size, characteristically occupy one hemi-thorax and several litres of pleural fluid may be aspirated [13]. Often, there are no other parenchymal features seen radiologically and the absence of pleural thickening, mediastinal or pulmonary adenopathy on thoracic CT does not exclude the diagnosis particularly in primary disease. The pleural fluid is often straw coloured on thoracocentesis though it may be blood-stained.

In the absence of anti-tuberculous chemotherapy, resolution of the effusion usually occurs spontaneously within several months trapping the unwary clinician. However, half of such untreated cases go on to develop more severe forms of pulmonary or extra-pulmonary tuberculosis which may result in severe disability or death. The most compelling evidence for this is described in detail by Patiala who followed the course of TB pleuritis in 2816 men from the Finnish army for a period up to 9 years [6]. 43% of all those followed developed post-pleural pulmonary tuberculosis and the mortality in this group was 37.3%; 75% of these cases did so within a 2 year period. 70% of cases were pulmonary in origin and it was also concluded that progression was seen more frequently in urban settings, if the age of onset of pleural tuberculosis was higher and in those with a family history of tuberculosis.

Other sequelae of primary tuberculous pleurisy are the development of residual pleural thickening and the potential to cause ventilatory limitation. This has been reported in up to 50% of patients by various authors though the incidence of this complication can be reduced significantly by appropriate anti-tuberculous chemotherapy [14-16]. Barbas et al in a study of 44 patients concluded that clinical presentation, symptoms and biochemical analysis of the pleural fluid could not reliably predict the occurrence and extent of residual pleural thickening following chemotherapy though weight loss & cough were more common presenting features in those with residual pleural changes [16]. However, De Pablo et al noted that residual pleural thickening of 10mm was associated with a lower pleural fluid pH and glucose levels at presentation (i.e. a more substantial inflammatory pleural response) in a study of 56 patients [17].

Chronic pleural infection with larger numbers of bacilli in post-primary or "re-activation" disease is associated with greater respiratory and systemic symptoms, weight loss and radiographic abnormalities. Radiologically, there may be evidence of parenchymal cavitory lung disease or infiltrates though again, the radiological findings may be non-specific.

A loculated pleural effusion on CT scanning associated with pleural thickening, enlargement of the overlying ribs and a calcified pleural rind suggests the presence of a tuberculous empyema. Tho-

racocentesis here may yield purulent fluid. In some cases, the inflammatory process may have been present for many years before the patient seeks medical attention due to the containment of tubercle bacilli in a cavity encased by thickened pleura. However, patients may present dramatically with a broncho-pleural fistula, pyopneumothorax and empyema necessitates. In the latter scenario, the empyema erodes through the parietal pleura into surrounding structures and organs commonly resulting in a chest wall mass. Complications of tuberculous empyema include malignant transformation, pleural aspergillosis and superior vena cava syndrome. Later sequelae of tuberculous empyema also include the development of significant pleural thickening and fibrosis resulting in restrictive ventilatory abnormalities seen in later life [55].

Patients may also present many years after an initial illness with a post-tuberculous chronic empyema. Such cases may have a history of thoracoplasty, artificial pneumothorax, collapse therapy or inadequate chemotherapy regimens. Cases of tuberculous pseudochoylothorax are seen rarely as a complication of chronic pleural thickening [18].

Diagnostic methods in tuberculous pleural disease

Perhaps the most valuable tool to the clinician in diagnosing tuberculous pleurisy is to maintain an index of suspicion for tuberculosis in a patient presenting with an exudative pleural effusion. This is particularly relevant in developed countries in the western world where malignancy is a more common cause of such a presentation and the diagnosis of tuberculosis may be overlooked. Pleural effusions presenting in immigrants from countries with a high TB burden should be regarded as tuberculous in aetiology until proven otherwise.

Biochemical and cellular analysis of pleural fluid

Thoracocentesis of a primary tuberculous pleural effusion characteristically yields an exudate with a total pleural fluid protein greater than 30 g/dl, pleural fluid to serum LDH ratio >0.5 and total pleural fluid LDH >200U. The pleural fluid is lymphocyte predominant (often exceeding 75% of all cellular material) often with a reduced glucose concentration [19]. Unfortunately, none of the above features are specific for tuberculosis and similar pleural fluid characteristics are seen in parapneumonic effusions, some malignancies and rheumatoid disease involving the pleura and additional tests are required in most cases. The presence of significant mesothelial cells or in the pleural fluid argues against tuberculous pleurisy and should prompt the investigating clinician to consider an alternative diagnosis [20].

Microbiological analysis of pleural fluid

Tuberculous pleural effusions represent an immunological reaction to relatively few acid-fast bacilli in the pleural space. Loddenkemper report-

ed pleural fluid cultures being positive in 28% of cases whilst Berger reported 30% positive cultures [21, 22]. Bedside inoculation of pleural fluid with non-radiometric culture media e.g. BACTEC has been reported to increase the yield of positive cultures [23]. One study of thoracoscopically collected samples reported that the yield from pleural fluid cultures improved when the pleural fluid glucose concentration fell below 50 mg/dl (59 v 25%) [21]. However, a consistent finding in the literature is that microscopy and culture for pleural fluid is negative in a large number of cases and does not exclude tuberculous pleurisy. Thus additional investigations are recommended in most cases to establish the diagnosis.

Tuberculosis should always be considered in the differential diagnosis of an empyema where the diagnosis is often made by microscopy & culture of the purulent pleural fluid obtained from thoracocentesis. The yield from pleural fluid is higher in tuberculous empyema as this represents infection of the pleural cavity with a higher bacillary load [18, 23, 24].

Closed "blind" pleural biopsy for histology and culture

Closed needle biopsy is frequently performed as an investigation for the diagnosis of pleural tuberculosis and the diagnostic yield exceeds that of culture of pleural fluid alone. Closed or "blind" percutaneous pleural biopsy can be performed simply as a bedside test in those areas which have limited access to health care resources and in particular more invasive, expensive techniques such as medical thoracoscopy or surgical biopsy.

It is recommended that at least 6 biopsy specimens are taken in order to obtain a representative sample of parietal pleural tissue [25]. Histopathological analysis of pleural biopsy specimens may reveal granulomatous inflammation though this can also be seen in cases of fungal infections, sarcoidosis or rheumatoid disease involving the pleura [18].

In a study of 42 patients with tuberculous effusions, closed needle biopsy achieved a diagnostic sensitivity of 79% when histology and culture were combined with a specificity of 100%. Histology alone gave a diagnostic sensitivity of 67% [26]. Seibert et al reported a yield of 66.7% from closed pleural biopsy cultures and 84.6% from histology [9]. Pleural tissue simultaneously sent for mycobacterial culture in addition to histology may increase diagnostic yield further. The diagnostic yield has been reported to rise to 90% when closed pleural biopsies are cultured [27].

Thoracoscopic pleural biopsy

Closed needle biopsy is being superseded by more high-technology techniques such as image-guided and thoracoscopic pleural biopsies which have been shown to be superior to the blind Abrams biopsy in terms of diagnostic sensitivity [28]. Thoracoscopy has provided the means to directly visualize the pleural abnormalities hence improving the yield of any pleural biopsy. This is

particularly applicable in cases where pleural involvement is patchy and may be missed by blind biopsy alone. The sensitivity of thoracoscopic pleural biopsy in the diagnosis of pleural tuberculosis exceeds 90% in a number of studies [29-31]. One study reported that thoracoscopy had a diagnostic sensitivity of 100% when pleural biopsy histology and culture specimens were taken in combination [26]. However, thoracoscopy may not always be feasible in many high prevalence areas due to lack of resources and closed needle biopsy still plays a significant diagnostic role under these circumstances.

Pleural fluid Adenosine deaminase (ADA) and Interferon- γ (IFN- γ) levels

ADA is an enzyme concerned with purine catabolism and higher levels are seen in lymphocytes. There is a positive relationship between ADA levels and pleural fluid CD4+ cells as well as lymphocyte differentiation [32].

There has been considerable interest in measuring the concentration of pleural fluid ADA and IFN- γ in tuberculous effusions in order to serve as a diagnostic aid. A clinical application to this is whether the levels of these substances in conjunction with other parameters in pleural fluid could discriminate between tuberculous and non-tuberculous effusions in the absence of histopathological support or a microbiological diagnosis. This becomes more relevant in areas with a higher disease prevalence and burden, which may also lack access to more invasive diagnostic facilities.

In a recent South African study of 51 patients with exudative pleural effusions (42 tuberculous effusions, 5 malignant, 4 idiopathic) the sensitivity of pleural fluid ADA alone in tuberculous effusions was 95% using a cut off value of 50 U/l with a specificity of 89%. The specificity improved to 100% when this was combined with a Lymphocyte/Neutrophil (L/N) ratio >0.75 but the sensitivity fell to 89%. In this study, combining blind Abrams biopsy, ADA >50 U/l and L/N ratio >0.75 achieved a sensitivity of 93% and a specificity of 100% [26]. Another study from a high prevalence region also reported similar results when the pleural fluid L/N ratio >0.75 was combined with ADA levels >50 U/l [33].

However, ADA is also raised in pleural malignancies, lymphoproliferative diseases and rheuma-

toid disease hence giving rise to false-positives [34-36]. This becomes particularly relevant in those areas where there is a lower prevalence of Tuberculosis and where a substantial proportion of exudative pleural effusions are diagnosed as being due to malignancy.

The use of pleural fluid ADA levels in order to exclude the diagnosis of tuberculosis has also been examined. In a South African study in 1996, 303 patients with exudative pleural effusions were studied of which 143 (58%) were tuberculous in aetiology and 59 (19%) malignant [33]. Pleural fluid ADA was noted to be less than a cut off figure of 50 U/l in 13 tuberculous pleural effusions. Combining an ADA level of 50 U/l and L/N >0.75 in diagnosing tuberculous pleurisy achieved a sensitivity of 88% and a specificity of 95% this study. The use of isoenzymes of ADA in pleural fluid has not been found to be particularly helpful as a diagnostic aid [37].

The majority of studies assessing the effectiveness of ADA in the diagnosis of tuberculous pleuritis were performed in high prevalence areas on a relatively young patient population (see table 2). One study in a low prevalence tuberculosis area appeared to show a reduction in specificity of pleural fluid ADA compared to that seen in higher prevalence regions [41]. A met analysis of 31 studies (4738 patients in total) published in 2003 reported a maximum joint sensitivity and specificity of 93% for pleural fluid ADA [40]. Further and larger studies, including patients of all age groups and areas of low disease prevalence are needed.

The measurement of IFN- γ levels in pleural fluid has been studied. In 140 patients with exudative pleural effusions (32 diagnosed as definite pleural TB and 19 as probable pleural TB), IFN- γ (Using a cut off value of 140 pg/ml in pleural fluid) had a sensitivity of 85.7%, which was less than that of ADA but was found to be more specific at 97.1% in those patients with a definitive diagnosis [42]. A met analysis of 13 studies (1189 patients) arrived at a maximum joint sensitivity and specificity of 96% for pleural fluid IFN- γ in tuberculous pleural effusions [40].

The role of PCR in the diagnosis of tuberculous pleural disease

The potential of DNA amplification techniques to rapidly detect Mycobacterium tuberculosis in

Table 2. - The role of pleural fluid adenosine deaminase (ADA) in the diagnosis of tuberculous pleurisy

Author	Number of patients	ADA "Cut off" value used (IU/l)	Sensitivity of ADA (%)	Specificity of ADA (%)
Diacon et al [26]	51	50	95	89
Burgess et al [39]	462	50	90	89
Valdes et al [35]	129	47	100	87.5
Villegas et al [42]	140	45.5	88	85.7
Chen et al [38]	210	55.8	87.3	91.8
Burgess et al [33]	472	50	91	81

pleural fluid and biopsy specimens has been widely explored. Regarding the role of pleural fluid PCR, the sensitivities reported in the literature vary from 20 to 81% and specificities ranging from 78 to 100% [43, 44]. In the study by Villegas et al, examining a group of 32 patients with definitive pleural TB, pleural fluid PCR had a sensitivity of 73.8%, specificity of 90%, positive predictive value of 81.6% and a negative predictive value of 85.1%. However, when taking those cases with confirmed and probable pleural TB, the sensitivity dropped to 60.7%. There were 7 false positives seen (In 3 idiopathic effusions and 4 others) overall. When pleural fluid PCR for TB was combined with ADA and IFN- γ as a diagnostic tool in the study, this resulted in an increase in the overall sensitivity and specificity [42].

PCR has also been applied to pleural biopsy specimens. In a small study of 28 patients in Japan (19 TB effusions, 9 other), 17 of the 19 cases of TB pleurisy were positive for PCR on pleural biopsy specimens resulting in a sensitivity of 89%. There were no false positives seen resulting in a specificity of 100%. In this study, both the false negative PCR pleural biopsy specimens revealed granulomatous changes on histology and the authors suggest combining PCR with microbiological and histological examination of pleural biopsy specimens to improve diagnostic yield further [45]. An Egyptian study recommended PCR of pleural biopsy specimens as a rapid diagnostic test, finding that PCR when applied to pleural biopsy specimens in tuberculous pleurisy reached a sensitivity of 90%, specificity of 100% and a negative predictive value of 86.6%. In this study the diagnostic accuracy of PCR was similar to that to culture of closed needle biopsy samples [46].

The role of sputum smears and cultures in diagnosing pleural tuberculosis

The yield of sputum smears and cultures in tuberculous pleural effusions is lower in the absence of parenchymal infiltrates (primary TB pleurisy) compared to post-primary disease. Seibert et al reported positive sputum cultures in 11.4% of those cases without pulmonary infiltrates in their series [9]. In a Spanish study, only 2% of those with primary disease had positive sputum smears and 7% having positive cultures which contrasted with 16% of "re-activation" disease being smear positive and 28% culture positive [47]. The findings contrast with a study by Conde et al where the yield from sputum induction was 55% in those tuberculous effusions with no parenchymal radiographic abnormalities [48].

In essence, the absence of a positive sputum smear and culture results does not exclude the diagnosis of tuberculous pleural disease and should not dissuade the investigating clinician to perform a pleural biopsy for histology and culture.

Tuberculin skin testing in pleural tuberculosis

A widespread immunological response to the bacillus occurs and one consequence of such a re-

sponse is often seen in terms of a strongly positive tuberculin skin test. Activation of T-lymphocytes (mainly CD4+) occurs following exposure to those macrophages sensitised to the mycobacterial antigen and such lymphocytes predominate in the pleural space within days following the initial infection. The mechanism underlying tuberculin skin test reactivity in pleural tuberculosis lies in the production of cytokines such as IFN- γ and interleukin-2 by activated pleural T-lymphocytes. Such cytokines are involved in further enhancing macrophage function and regulation of T-lymphocyte numbers. These hypersensitivity phenomena occur peripherally (e.g. in the skin and bloodstream) as well as in the pleural space resulting in the detection of a positive tuberculin skin test in clinical practice [18].

However, false-negative tuberculin skin tests in tuberculous pleurisy are also observed and this has been explained by the confinement of appropriately sensitised T-cells inside the pleural space [23]. Under such circumstances, despite mycobacterial infection, a peripheral hypersensitivity reaction does not take place resulting in an absence of tuberculin skin test reactivity.

The sensitivity of tuberculin skin testing varies in the literature. Seibert et al reported a sensitivity of 93% in 43 tuberculous effusions in terms of tuberculin skin test reactivity [9]. However; lower values have also been noted with false negative rates of 30% and higher reported in the literature particularly in the elderly [23, 47, 49]. In addition, false negative skin tests are seen more frequently in the context of HIV co-infection [50].

It is not certain whether tuberculin skin reactivity is influenced by primary or secondary disease. Arriero et al noted that a positive skin test (defined as induration >9 mm after 48-72 hrs) was seen in 60% of primary effusions and 47% of secondary effusions though this did not reach statistical significance [47].

In practice at least 90% of tuberculous effusions can be diagnosed by obtaining pleural fluid and biopsy smear, culture and histology. However, there may be a role for tuberculin skin testing in younger patients presenting with suspected tuberculous pleural disease after pleural fluid and biopsies are non-diagnostic and a trial of anti-tuberculous chemotherapy is being considered [23].

Management of tuberculous pleural disease

Standard anti-tuberculous chemotherapy

The diagnosis of tuberculous pleural effusion is an indication for treatment with anti-tuberculous chemotherapy. Standard short course chemotherapy with isoniazid, rifampicin, pyrazinamide and ethambutol followed by 4 months of isoniazid and rifampicin is sufficient in the majority of cases [51]. Following the initiation of the standard 4 drug regimen mentioned, subsequent treatment should be guided according to the results of drug sensitivity testing when they become available to

the clinician. The incidence of residual pleural thickening and the functional sequelae can be reduced by effective anti-tuberculous chemotherapy [15]. Although studies by Dutt et al supported the effectiveness of a 6 month regimen of isoniazid and rifampicin in both pulmonary and pleural disease, this is generally not advised due to the problems associated with drug-resistance [52]. Paradoxical enlargement of the effusion has been reported after the commencement of anti-tuberculous chemotherapy similar to that seen in intra-cranial tuberculomas and this can require drainage for symptom relief on occasion [53].

The role of corticosteroids in tuberculous pleural disease

The place of corticosteroids in the treatment of pleural tuberculosis remains contentious. Lee et al in a study of 40 patients concluded that the addition of corticosteroids in tuberculous pleurisy led to a more rapid resolution of the effusion and of clinical symptoms, in particular, fever [54]. A Spanish study compared 117 patients (57 received prednisolone; 60 had placebo) with tuberculous effusions. Although it was observed that there was more rapid resolution of pleural fluid in the prednisolone group after one month, there was no difference seen by the end of the study (46 months) and neither was any difference seen in the degree of residual pleural thickening or lung function [55]. Wyser et al in a study of 70 patients in South Africa (34 received prednisolone; 36 received placebos) similarly concluded that there was no benefit seen with corticosteroids in terms of pleural complications such as pleural thickening, lung function impairment or in terms of earlier symptom relief [15]. A Cochrane review in 2000 concluded that there was insufficient evidence to conclude that corticosteroids were effective in tuberculous pleurisy [56].

Drainage of the pleural cavity

Although Wyser et al recommend that early complete drainage of the pleural space should be carried out in addition to the patient receiving anti-tuberculous chemotherapy; this has been challenged by other authors [15].

A recent study of 61 patients from Taiwan evaluated the role of pig-tail drainage of the pleural cavity in tuberculous pleural effusions in addition to standard anti-tuberculous chemotherapy. Although there was an improvement in terms of resolution of dyspnoea score in the "drainage" arm (4 vs. 8 days), there was no difference observed in the incidence of residual pleural thickening, resolution of fever or any other clinical symptoms [57]. It is thus recommended that moderate or large sized tuberculous effusions are drained or aspirated for symptomatic purposes only if required in addition to instituting anti-tuberculous treatment.

Management of tuberculous empyema and other complications

Fortunately, tuberculous empyema is rare in the western world compared to primary tuberculous effusions representing chronic active infection of the pleural space with larger numbers of bacilli. A study of 26 cases of tuberculous empyema in Saudi Arabia revealed that patients presented with respiratory symptoms for a mean period of 4.43 months (range 1-48 months) and the mean age of presentation was 33.8yrs (Age range 18-61 years) [58].

Tuberculous empyema should be managed in a similar fashion to any other empyema with intercostal tube drainage of pus, appropriate anti-tuberculous chemotherapy and the consideration of surgical intervention if conservative measures are unsuccessful. The concentration of anti-tuberculous drugs has been shown to be lower in the pleural space and the issue of developing drug resistance has been raised. Decortication and other surgical procedures including pneumonectomy may be performed as a curative measure as well as to address the presence of significant pleural thickening which may impair re-expansion of the trapped lung and cause ventilatory limitation [59].

The impact of HIV co-infection on tuberculous pleurisy

HIV represents the strongest risk factor for the development of active tuberculosis in those with latent disease. Worldwide, HIV co-infection has impacted significantly on the tuberculosis epidemic with HIV positive individuals with latent tuberculosis infection having a 10% annual risk of developing clinically active disease compared to a 10% lifetime risk seen in immunocompetent persons. A study of 127 cases of pleural effusion in Rwanda revealed tuberculosis to be the aetiology in 86% and of the 98 cases tested, 83% were HIV positive [60] and others have reported similar results in terms of the prevalence of HIV co-infection and pleural TB in Africa [66]. In a Brazilian study of 43 patients with tuberculous pleurisy, there was a 30% prevalence of HIV co-infection [61].

A number of studies suggest an increased incidence of pleural involvement in AIDS cases diagnosed with active tuberculosis. In a study comparing 963 HIV positive adults with pulmonary TB with 1000 HIV negative age-matched controls; there was a significantly higher incidence of pleural effusions (16 vs. 6.8%) [62]. In the western world, a study in South Carolina, USA appeared to show increased rates of pleural TB in AIDS cases (11%) compared to non-AIDS cases (6%) [63].

There is also evidence to suggest that HIV co-infection alters the clinical presentation of TB pleurisy. The duration of the presenting illness tends to be longer in a substantial number of such cases compared with that seen in HIV negative individuals. A study from Tanzania found that HIV positive patients tend to present with more constitutional symptoms such as dyspnoea, fevers, night sweats,

fatigue and diarrhoea with hepatosplenomegaly and lymphadenopathy being more frequent clinical findings. A negative mantoux test, lower haemoglobin values as well as lower pleural fluid albumin levels were also seen more frequently though there were no radiological differences observed [64]. Other studies observed atypical radiological features in HIV co-infected TB pleurisy cases, in particular the finding of a predominance of lower lobe pulmonary infiltrates [63]. One study reported a higher yield from pleural biopsy cultures in HIV positive individuals (69% compared to 21% seen in HIV negative persons) suggesting a higher pleural bacillary burden. The same study also reported that only 41% of the HIV positive group exhibited a positive tuberculin test as opposed to 76% of the HIV negative group [50]. However, another study found that HIV co-infection made no difference in terms of pleural biopsy yield [65].

The relationship between the CD4 count in HIV infected individuals and the biochemical characteristics of the pleural fluid in tuberculous effusions has also been examined. In a study of 19 cases of HIV co-infected pleural tuberculosis, 10 (53%) were found to have a CD4 count >200/ μ l and no significant differences in pleural fluid characteristics were found in those patients presenting with a CD4 count greater or less than 200/ μ l [65]. A prospective study in 2 Harare hospitals observed no relationship between CD4 count and pleural granulomata formation suggesting that an active immune system in the pleural space even in advanced cases of HIV. In the same study, CD4 counts < 200/ μ l was associated with positive pleural fluid smear and biopsy as well as a longer duration of illness [66].

Treatment of tuberculous pleurisy in HIV positive co-infection is generally successful with a good outcome in most cases. In a series of 22 patients, there were 2 deaths reported and only 1 after anti-tuberculous chemotherapy was commenced [62].

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