SERIES 'THE PLEURA'
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Pleural tuberculosis

J. Ferrer

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ABSTRACT: Tuberculous pleural effusions occur in up to 30% of patients with tuberculosis. It appears that the percentage of patients with pleural effusion is comparable in human immunodeficiency virus (HIV)-positive and HIV-negative individuals, although there is some evidence that HIV-positive patients with CD4+ counts <200 cells·mL^{-1} are less likely to have a tuberculous pleural effusion.

There has recently been a considerable amount of research dealing with the immunology of tuberculous pleurisy. At present, we have more evidence that activated cells produce cytokines in a complex pleural response to mycobacteria. Intramacrophage elimination of mycobacterial antigens, granuloma formation, direct neutralization of mycobacteria and fibrosis are the main facets of this reaction.

With respect to diagnosis, adenosine deaminase and interferon gamma in pleural fluid have proved to be useful tests. Detection of mycobacterial deoxyribonucleic acid (DNA) by the polymerase chain reaction is an interesting test, but its usefulness in the diagnosis of tuberculous pleurisy needs further confirmation. The recommended treatment for tuberculous pleurisy is a 6 month regimen of isoniazid and rifampicin, with the addition of pyrazinamide in the first 2 months. HIV patients may require a longer treatment. The general use of corticosteroids is not recommended at this time, but they can be used in individuals who are markedly symptomatic.
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Correspondence: J. Ferrer
Servei de Pneumologia
Hospital General Universitari Vall d'Hebron
E-08035 Barcelona
Spain

Incidence

The clinical importance of tuberculosis in general and of tuberculous pleural effusion in particular is not the same worldwide. Of the 8 million people who developed tuberculosis in 1990, 95% lived in developing countries [1]. In sub-Saharan Africa, 15 million new cases of tuberculosis are expected over the next 5 yrs [2]. The frequency of pleural effusion in these tuberculous patients is currently approximately 31% [3].

It seems that co-infection with human immunodeficiency virus (HIV) is the main factor responsible for this increase in tuberculosis and tuberculous pleurisy. In Burundi and Tanzania, 60% of patients with tuberculous pleural effusion were HIV-positive [3, 4]. Initial data suggest that HIV patients tend to develop tuberculous pleurisy in the early stages of immunosuppression. In one report, the prevalence of pleural effusion in tuberculous HIV patients with CD4+ T-lymphocyte (helper-inducer) counts >200 cells·mL^{-1} was 27%, while it was only 10% in HIV patients with tuberculosis and CD4+ T-lymphocyte counts <200 cells·mL^{-1} [5]. There are contradictory data regarding the frequency of pleurisy in HIV-positive and HIV-negative patients with tuberculosis. One study in South Africa reported a higher frequency in HIV-positive patients [6], but several other studies in Central Africa could find no such differences [3, 4]. The fact that HIV infection affects mainly young adults could explain the high frequency of pleurisy in HIV patients with tuberculosis, since young people tend to have primary disease.

Pathogenesis

The current hypothesis for the pathogenesis of primary tuberculous pleural effusion is that a subpleural caseous focus in the lung ruptures into the pleural space 6–12 weeks after a primary infection [7]. Mycobacterial antigens enter the pleural space and interact with T-cells previously sensitized to mycobacteria, resulting in a delayed hypersensitivity reaction and the accumulation of fluid. It seems that this reaction of the pleura augments the entry of fluid into the pleural space by increasing the permeability of pleural capillaries to serum proteins [8], and thereby increasing the oncotic pressure in the pleural fluid. Involvement of the lymphatic system probably also contributes to the accumulation of pleural fluid. An impaired clearance of proteins from the pleural space has been reported in human tuberculous effusions [9]. It is known that the clearance of proteins and fluid from the pleural space is carried out by lymphatics in the parietal pleura. Fluid gains access to the lymphatics through openings in the parietal pleura

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called stomata [10]. Since the parietal pleural is diffusely affected with pleural tuberculosis, damage to or obstruction of the stomata could be an important mechanism leading to accumulation of pleural fluid.

Immunology

It appears that tuberculous pleurisy is due to a delayed hypersensitivity reaction rather than to a tuberculous infection. This hypothesis is supported by several facts. Cultures of pleural specimens from patients with tuberculous pleurisy are frequently negative [11]. A lymphocytic pleurisy can be produced in sensitized guinea-pigs by the intrapleural instillation of heat-killed bacilli Calmette-Guérin (BCG) [12]. Moreover, pleural effusion also develops in nonsensitized animals who have received cells from immunized animals [13]; and effusion does not develop in sensitized animals if they are given anti-lymphocyte serum [14].

Neutrophils appear to be the first cells responding to mycobacterial protein in the pleural space. In an animal model of purified protein derivative (tuberculin) (PPD)-induced pleural effusion, neutrophils initially predominate and are responsible for the recruitment of blood monocytes [15]. Recent studies suggest that the mesothelial cell plays a role in the recruitment of blood neutrophils and monocytes in tuberculous pleuritis [16]. After 3 days, lymphocytes are already predominant in the tuberculous pleural fluid [12]. Most of the lymphocytes in a tuberculous pleural effusion are T-lymphocytes [17]. Lymphocytes are mainly CD4+ [17], with a mean CD4:CD8 (helper:suppressor) ratio of about 4.3 in pleural fluid, and 1.6 in peripheral blood [18].

Recent studies provide a partial explanation of the immunological process in tuberculous pleurisy. After phagocytosing mycobacteria, macrophages act as antigen-presenting cells to the T-lymphocytes, which become activated and promote differentiation of macrophages and granuloma formation. Some components of the mycobacterial cell wall, such as protein/proteoglycans complex and lipoarabidomannan, are able to stimulate macrophages to produce tumour necrosis factor (TNF), a regulator of granuloma formation [19]. Activated pleural macrophages can also produce interleukin-1 (IL-1) [20]. Both TNF and IL-1 are involved in lymphocyte activation. Upon exposure to PPD, pleural T-lymphocytes from patients with tuberculous pleurisy produce more interferon-γ (IFN-γ), an important activator of macrophage killing capacity [21], and interleukin-2 (IL-2), a regulator of T-cell proliferation, than do peripheral blood T-lymphocytes from the same individuals [20, 22]. Pleural fluid activated T-cells producing IFN-γ have been phenotypically qualified as CDW29+ [23]. Interestingly, CDW29+ T-cells predominate in the core of tuberculous granulomas [23]. It seems, however, that only a minority of CD4+ T-cells are functionally active at the same time [24]. Cytotoxic cell activity could be an additional defensive mechanism against mycobacteria. Pleural fluid CD4+ [25] and pleural natural killer (NK) T-cells [26] of tuberculous patients have both shown cytotoxic activity when stimulated with PPD.

As in the pleura, the cutaneous response to PPD is promoted by IL-2 and IFN-γ [27], which are produced by CD4+ cells. Paradoxically, however, up to 30% of patients with tuberculous pleurisy have a negative PPD test [11]. Since adherent suppressor cells are found in the peripheral blood but not in the pleural fluid of tuberculous patients [17], these cells could suppress the activity of blood T-lymphocytes in tuberculin anergic patients. However, peripheral suppressor cells cannot be detected in some PPD-negative patients with pleural tuberculosis. The PPD negativity in these patients has been attributed to compartmentalization of CD4+ T-lymphocytes in the pleural space [17].

Diagnosis

It appears that in developed countries tuberculous pleurisy is becoming a form of reactivation rather than primary disease [28], and therefore the mean age of the affected individual is much higher than it was 50 yrs ago [28]. The diagnosis of tuberculous pleurisy in older individuals can be problematical, because these patients tend to have other conditions that could be responsible for their pleural effusions, such as pleural malignancy. Moreover, patients with tuberculous pleurisy do not have distinctive clinical symptoms. Fever, chest pain, weight loss and other symptoms are present in patients with tuberculous pleurisy as well as in patients with exudative effusions with other aetiologies. Initial data suggest that patients with tuberculous pleural effusion and HIV seropositivity have been symptomatic for a longer period, have additional symptoms (tachypnoea, fever, dyspnoea, night sweat, fatigue, diarrhoea), and have more hepatomegaly, splenomegaly and lymphadenopathy than patients who are seronegative [29].

Tuberculin skin test

The diagnostic evaluation of patients with tuberculous pleurisy includes a tuberculin skin test. In populations with a high prevalence of tuberculous infection, a positive skin test in a patient with a pleural exudate strongly suggests the diagnosis of tuberculosis, whereas the diagnostic value of a positive tuberculin skin test in countries with a low prevalence of tuberculous pleurisy is lower. On the other hand, a negative tuberculin skin test does not rule out the diagnosis of tuberculous pleurisy. Negativity of the skin test has been reported in up to 30% of immunocompetents [11], and in up to 59% of HIV-infected patients [30]. The explanation for the negative tuberculin skin test is outlined above.

Diagnostic tests

The stepwise diagnosis of tuberculous pleurisy is the same as for any other pleural exudate. An initial diagnostic thoracentesis is always indicated. The fluid from patients with tuberculous pleurisy is an exudate rich in lymphocytes with less than 5% mesothelial cells [31]. However, these studies, in conjunction with measurement of the pleural fluid glucose and lactic dehydrogenase level, do not definitely discriminate tuberculous pleurisy from other exudates.

A definite diagnosis of tuberculous pleurisy is achieved when *Mycobacterium tuberculosis* is demonstrated in sputum or pleural specimens, or when caseous granulomas are found in pleural biopsies. The sputum cultures are positive in 30–50% of patients with both pulmonary and pleural tuberculosis [11, 32], but are positive in only 4% of patients with isolated pleural effusion [33]. For the diagnosis of tuberculous pleurisy, the sensitivity of pleural fluid culture is 10–35% [11, 32, 33], needle pleural biopsy between 56–82% [32, 33], and needle pleural biopsy culture between 39–65% [11, 33]. It seems that the use of the radiometric mycobacterial culture system (BACTEC) could overcome the problem of the delay of the culture results. Positive cultures can be obtained in 18 days with the BACTEC system, compared with the 33 days with the conventional method [34]. Moreover, it appears that the sensitivity of mycobacterial cultures can reach 50% if bedside inoculation of pleural fluid is substituted for laboratory inoculation [34].

At least four separate biopsy specimens of parietal pleura should be obtained. Three should be sent for histological studies and the other one should be cultured for mycobacteria [8], since the pleural biopsy culture is sometimes positive when there are no granulomas in the pleura [11]. With both histological and microbiological studies of pleura, diagnostic yields as high as 86% have been reported [32]. A diagnostic thoracoscopy is needed only occasionally to make the diagnosis of tuberculous pleurisy. In a recent study, the diagnostic yield of Abrams needle biopsy and thoracoscopy was prospectively evaluated in 40 patients with tuberculous pleurisy [35]. Sensitivity of Abrams biopsy, combining histology and culture, was 86%, while that for thoracoscopy was 98%. There were seven patients with negative needle biopsies, who were diagnosed by thoracoscopy.

There is a little information on the diagnostic yield of the different tests in the diagnosis of tuberculous pleurisy in HIV-infected patients. Initial data suggest that HIV patients have a higher incidence of positive sputum culture for *M. tuberculosis,* but a similar incidence of positive pleural tissue cultures or pleural granulomas to HIV negative patients [30]. There is no information on the yield of the different diagnostic techniques in HIV patients with tuberculous pleurisy and their relationship to CD4+ counts. It would be reasonable to hypothesize that HIV patients with a CD4+ count <200 cells·mL^{-1} would have greater difficulty in controlling the mycobacteria. In these patients, therefore, the yield of pleural histology would be lower and the positivity of the pleural fluid and tissue cultures would be higher than in HIV-negative patients, but this hypothesis still remains unproven.

New diagnostic parameters

Histological examination of pleura by needle biopsy is not conclusive in 20–40% of patients with tuberculous pleuritis [32, 33]. When the pleural biopsy is negative, mycobacteria can be cultured in pleural specimens in less than 10% of patients [32], and this usually takes at least 3 weeks. Several new laboratory tests on pleural fluid have been proposed to make an early diagnosis of tuberculous pleurisy.

Most interest has been focused on adenosine deaminase (ADA). ADA is the enzyme that catalyses the conversion of adenosine and deoxyadenosine to inosine and deoxyinosine, respectively. Tuberculous pleural fluid contains higher levels of ADA than do most other exudates [36, 37], but elevated pleural fluid ADA levels do occur with most empyemas [36], some lymphomas [36], rheumatoid pleurisy [38] and, rarely, with nonlymphoma malignancies [36] and intracellular infections [39]. ADA has recently been separated into ADA1, which is found in all cells and is composed of 2 dimers, ADA1m and ADA1c, and ADA2, which reflects monocyte/macrophage activation. Patients with tuberculous pleurisy had predominantly ADA2, whilst those with empyema and parainfective effusions had mainly ADA1 [40].

The usefulness of ADA in the diagnosis of tuberculous pleurisy depends on the prevalence of tuberculosis. In populations with a high prevalence of tuberculous pleurisy, the sensitivity and specificity of ADA are approximately 95 and 90% respectively [36, 37]. In contrast, in countries with a low prevalence of tuberculous pleuritis, the specificity of ADA can be considerably lower [41], although the determination of ADA isoenzymes could overcome this problem.

What is the current role of ADA in the diagnosis of tuberculous pleurisy? If we consider young people, a recent study in Galicia, Spain, has reported some interesting data. Sixty three percent of pleural effusions in patients less than 35 yrs of age were tuberculous, whereas only 7% were malignant. Excluding empyemas, all patients with ADA levels higher than 47 U·L^{-1} had tuberculosis [42]. Bearing these results in mind, antituberculosis treatment can reasonably be started in patients less than 35 yrs of age with a pleural exudate and ADA higher than 47 U·L^{-1}, if empyema is ruled out. Pleural biopsy could be omitted in these cases, because the probability of malignancy is extremely low.

In patients above 35 yrs of age, the probability of malignancy is considerably increased, and the diagnosis of tuberculous pleurisy should be established by microbiology or histology. However, the physician must often decide whether or not to start antituberculosis treatment if the patient does not have a definite diagnosis but there is a compatible clinical pattern, pleural lymphocytosis and positive PPD test. It has recently been reported that of 19 untreated patients with an undiagnosed pleural effusion, positive PPD test and ADA lower than 45 U·L^{-1}, none developed tuberculosis during a mean follow-up of 69 months [43]. Consequently, I consider that antituberculosis treatment should not be started in immunocompetent patients with an idiopathic pleural effusion and positive PPD test, if pleural fluid ADA is below 45 U·L^{-1}. However, if such patients have a pleural fluid ADA level above 47 U·L^{-1}, antituberculosis treatment is recommended.

When the many other laboratory tests for the diagnosis of tuberculous pleurisy are considered, IFN-γ is the only one with a yield comparable to ADA in the diagnosis of tuberculous pleurisy [36]. However, since determining IFN-γ is more expensive than ADA, there is no reason to recommend its application. Lysozyme was also proposed to be useful in the diagnosis of tuberculous pleuritis [44], but its utility appears to be lower than that both of ADA and IFN-γ [36].

Table 1. – Utility of PCR in the diagnosis of tuberculous pleurisy

First author	[Ref.] Year	TB/NonTB cases	DNA sequence amplified	PCR sensitivity %			PCR specificity %
				Overall	Positive PF culture	Negative PF culture	
DE WIT	[47] 1992	53/31	336 base pair repetitive sequence	81	-	-	78
DE LASSENCE	[48] 1992	14/10	IS6110 insertion sequence	60*	100	50	100
			65 XD mycobacterial gene	20	66	8	100
QUEROL	[49] 1995	21/86	IS6110 insertion sequence	81	100	60	98
KUWANO	[50] 1995	10/9	16S rRNA gene (nested)	-	-	30	100
			Bovine tuberculous MP 1370 gene (nested)	-	-	20	100

*: four samples were positive only when tested on multiple occasions. TB: tuberculous; PCR: polymerase chain reaction; DNA: deoxyribonucleic acid; rRNA: ribosomal ribonucleic acid; PF: pleural fluid.

The diagnostic utility of measuring antibodies to myco-bacterial antigens in pleural fluid has recently been investigated [45]. The levels of antimycobacterial antibodies in pleural fluid are higher in tuberculous pleural fluid than in other exudates. Unfortunately, the sensitivity and specificity of this test are not sufficient to recommend its clinical use.

Polymerase chain reaction (PCR) is based on amplification of mycobacterial deoxyribonucleic acid (DNA). In lung specimens, PCR can be performed rapidly and has a diagnostic yield comparable to culture [46]. PCR has also been used to detect mycobacterial DNA in pleural fluid. Its sensitivity in the diagnosis of tuberculous pleurisy ranges 20–81%, depending on the genomic sequence amplified and the procedure used in the extraction of DNA, with a specificity ranging 78–100% [47–50] (table 1). The parameter that determines the sensitivity of PCR is probably the number of bacilli in the sample of pleural fluid analysed. Series with a sensitivity of pleural fluid culture of as high as 69% report an 80% sensitivity of PCR [49]. PCR is positive in 100% of culture-positive tuberculous pleural fluids [49], and only in 30–60% of culture-negative pleural fluids [49, 50]. It therefore seems that PCR may have a diagnostic utility in selected cases, but its routine use cannot be recommended at this time.

Treatment

The mycobacterial burden with tuberculous pleuritis is low and tuberculous pleuritis tends to resolve spontaneously in most cases [51]. However, it was reported many years ago that 65% of untreated patients with pleural tuberculosis develop pulmonary tuberculosis in the next 5 yrs [51]. Because of the paucity of mycobacteria in patients with tuberculous pleuritis, patients can be successfully treated with two drugs to which their organisms are susceptible. The current recommendation [52] for all pulmonary and extrapulmonary tuberculosis is a 6 month regimen, as follows: a first phase of isoniazid (INH), rifampicin, and pyrazinamide for the first 2 months; a second phase of isoniazid and rifampicin for the next 4 months (2HRZ/4HR). Ethambutol should be added if one or more of the following criteria are met: more than 4% primary resistance to isoniazid; a previous treatment with antituberculosis medication; the patient is from a country with a high prevalence of drug resistance; or a previous exposure to a drug-resistant case. In all instances, drug sensitivities should be ordered to guide the continuation of the treatment. The efficacy of this regimen has recently been confirmed [53]. HIV-positive patients with tuberculous pleurisy should be treated with the regimen described above, but it is very important to assess the clinical and bacteriological response and to prolong the treatment if necessary [52].

Patients with tuberculous pleurisy have been successfully treated with a 6 month regimen, with only isoniazid and rifampicin [54]. However, it must be taken into account that such a regimen can only be applied in areas with a low percentage of mycobacterial resistance to isoniazid. An even shorter regimen of 4 months (2HRZ/2HR) has recently been attempted in patients with tuberculous pleurisy in South Africa [55]. Although preliminary data suggest that this regimen is effective, a longer follow-up is needed to verify its effectiveness.

As many as 50% of patients with tuberculous pleurisy develop pleural thickening 6–12 months after the beginning of the treatment [56], and an occasional patient has even been subjected to decortication [57]. It is not known why some patients develop pleural thickening, and there are no objective data available to determine whether measures, such as pleural fluid evacuation or respiratory physiotherapy, are useful in preventing this residual thickening. Repeated thoracocentesis does not appear to alter the degree of residual pleural thickening [57]. The administration of corticosteroids results in a faster normalization of body temperature, erythrocyte sedimentation rate and disappearance of fluid [58]. However, there is growing evidence that the long-term development of pleural thickening is not affected by corticosteroids [58]. Bearing in mind these data, a reasonable management of the patient with tuberculous pleurisy is to perform a therapeutic thoracocentesis, attempting to evacuate as much fluid as possible, initiate antituberculosis chemotherapy, and start the patient on a respiratory physiotherapy programme.

Pseudochylothorax

Pseudochylothorax is a rare complication of patients with chronic tuberculous pleuritis, especially those treated with artificial pneumothorax [59]. These patients have a thickened pleura that delays fluid reabsorption and

causes persistence of effusion, cell breakdown and accumulation of cholesterol. The pleural fluid in tuberculous pseudochylothorax is turbid or milky, and the cloudiness persists after centrifugation. Analysis of pleural fluid usually demonstrates triglyceride levels below 110 mg·dL^{-1}; but the cholesterol level is usually elevated above 200 mg·dL^{-1} and, frequently, there are cholesterol crystals. Tuberculous pseudochylothorax should be treated with the antituberculosis regimen outlined above, even if there is no evidence of active tuberculosis.

Tuberculous empyema

Tuberculous empyema is a rare complication of tuberculosis. It is characterized by the presence of thick pus and the visceral pleura is usually calcified. It occurs most commonly in patients who have undergone artificial pneumothorax or thoracoscopy [60]. Patients usually have concomitant evidence of pulmonary tuberculosis, and the pleural pus contains a large number of mycobacteria on staining for acid-fast bacilli (AFB). In addition to a standard antituberculosis regimen, these patients may require serial thoracocentesis, extrapleural pneumonectomy or thoracoscopy.

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