Tuberculous Pleurisy

A Study of 254 Patients

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Objectives: To determine the age at which tuberculous pleural effusions occur, the radiological and biochemical characteristics of the effusions, the sensitivities of the various diagnostic tests, and the utility of combining clinical, radiological, and analytic data in diagnosis.

Methods: We studied the case histories of 254 patients in whom tuberculous pleural effusions were diagnosed with certainty between January 1, 1989, and June 30, 1997, in a Spanish university hospital in a region with a high incidence of tuberculosis.

Results: The mean (±SD) age of the patients was 34.1 ± 18.1 years, and 62.2% were younger than 35 years. The effusion was on the right side in 55.9% of patients, on the left side in 42.5% of patients, and on both sides in 1.6% of patients. In 81.5% of patients, less than two thirds of the hemithorax was affected. Associated pulmonary lesions were detected in 18.9% of patients, of whom 14.6% exhibited cavitation. In 93.3% of the effusions, more than 50% of leukocytes were lymphocytes, and almost all had the biologic characteristics of exudates (98.8% had high total protein contents, 94.9% had high cholesterol levels, and 82.3% had high lactate dehydrogenase levels). All but 1 effusion (99.6%) had an adenosine deaminase (ADA) concentration higher than 47 U/L, 96.8% (123/127) of the effusions had high ADA2 levels, and 89% (73/82) of the effusions had high interferon gamma levels. Adenosine deaminase 2 contributed 72.2% ± 12.5% (mean ± SD) of total ADA activity. Total ADA activity was significantly correlated with ADA2 (r = 0.83) and with interferon gamma (r = 0.30) levels. Definitive diagnosis was based on the observation of caseous granulomas in pleural biopsy tissue samples in 79.8% of patients, on the results of biopsy cultures in 11.7% of patients, and on pleural effusion cultures in the remaining 8.5% of patients. Results of the tuberculin skin test were positive in only 66.5% of patients.

Conclusions: In these patients, lymphocyte-rich exudative pleural effusions occurred, on average, at a young age, with no preference for either the right or the left side; normally affected no more than two thirds of the hemithorax; and were generally unaccompanied by pulmonary infiltrates. High ADA concentration was a highly sensitive diagnostic sign and was caused by a rise in ADA2 concentration. The most sensitive criterion based on pleural biopsy was the observation of caseous granulomas, and culture of biopsy material further increased overall sensitivity. Negative skin test results were no guarantee of the effusion being nontuberculous. This, together with the low mean age of the patients and the low frequency of associated pulmonary lesions, suggests that tuberculous pleural effusion is a primary form of tuberculosis in this region.

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MYCOBACTERIUM tuberculosis invades the pleural cavity chiefly through rupture of subpleural caseous foci within 6 to 12 weeks after a primary infection. Bacillus protein antigens seem to induce a delayed hypersensitivity reaction that stimulates lymphocytes, which in turn release certain lymphokines that (1) activate macrophages against the mycobacterium and (2) alter the permeability of pleural vessels and affect the formation of granulomas.1 Tuberculous pleural effusion (TPE) is an acute granulomatous pleurisy caused by recent infection by the mycobacterium. Patients with TPE invariably have a small subpleural nodule of tuberculosis showing fibrous and granulomatous inflammation and clear signs of leakage into the pleural space.2 Although TPE can resolve spontaneously within a few weeks or months, about one third of persons with untreated TPE subsequently develop a more serious form of tuberculosis.3 In our region (Galicia, in the northwest part of Spain), TPE chiefly affects young adults and children,4 radiologically has no preference for either the right or the left side,5 and is generally unaccompanied by pulmonary lesions.

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Tuberculous pleural effusions are not always easy to diagnose because the standard criterion (the presence of a lymphocyte-rich exudate associated with case-
PATIENTS, MATERIALS, AND METHODS

We studied the case histories of all 254 patients in whom TPE was diagnosed with certainty in our center between January 1, 1989, and June 30, 1997. Pleural effusions were diagnosed as tuberculous if (1) caseous necrotic granulomas were found in pleural biopsy tissue samples, (2) Ziehl-Neelsen stains or Lowenstein cultures of effusion or biopsy tissue samples were positive, or (3) Ziehl-Neelsen stains or Lowenstein cultures of sputum samples were positive if the pleural effusion was accompanied by pulmonary infiltration. All possible cases that failed to satisfy one of these criteria were excluded from the study. In no case was definitive diagnosis arrived at via thoracoscopy or open lung biopsy.

The following variables or procedures were recorded for or performed in all patients: patient age and sex; risk factors for tuberculosis; posteroanterior and lateral chest radiography; concentrations of protein, lactate dehydrogenase, cholesterol, and ADA in pleural fluid; Ziehl-Neelsen staining in 248 patients (the other 6 patients had empyema); and sputum samples were studied by Ziehl-Neelsen staining, Lowenstein cultures, and histological examination in 248 patients (the other 6 patients had empyema); and sputum samples were studied by Ziehl-Neelsen staining and Lowenstein culture in 48 patients in whom pleural effusion was associated with pulmonary lesions.

RESULTS

The 254 patients with TPE comprised 154 men and 100 women, with a mean (±SD) age of 34.1 ± 18.1 years (35.7 ± 18.6 years for men and 31.5 ± 17.0 years for women). Figure 1 shows their distribution by age group. Approximately 158 (62.2%) of 254 patients were younger than 35 years. Risk factors for tuberculosis were detected in 49 patients (19.3%) as follows: alcoholism, 38 patients; human immunodeficiency virus, 4 patients; neoplasia, 4 patients; psychiatric disorders, 2 patients; and hepatic cirrhosis, 1 patient.

Radiological test results showed effusions on the right side in 142 patients (55.9%), on the left side in 108 patients (42.5%), and on both sides in 4 patients (1.6%). The effusion affected more than two thirds of the hemithorax in 47 patients (18.5%), between one third and two thirds of the hemithorax in 120 patients (47.2%), and less than one third of the hemithorax in 87 patients (34.2%). In 48 patients (18.9%), pleural effusion was associated with pulmonary lesions, which were in the right upper lobe in 20 patients, the left upper lobe in 17 patients, the right lower lobe in 5 patients, the left lower lobe in 5 patients, and the middle lobe in 1 patient; 7 (14.6%) of these 48 patients exhibited pulmonary cavitation.

Table 1 lists the cytologic and biochemical characteristics of the effusions. In 237 patients (93.3%), more than 50% of leukocytes were lymphocytes; in 241 patients (94.9%), cholesterol concentration was at least 1.42 mmol/L (55 mg/dL); in 251 patients (98.8%), protein concentration was at least 30 g/L; in 209 patients (82.3%), lactate dehydrogenase activity was at least 200 U/L; and in 253 patients (99.6%), ADA activity exceeded the diagnostic threshold of 47 U/L. In 123 (96.8%) of 127 patients in whom ADA2 activity was determined, the value was at least 40 U/L; and in 73 (89%) of 82 patients in
whom IFN-γ level was determined, the value was at least 140 pg/mL. Adenosine deaminase 2 contributed 72.2% ± 12.5% (mean ± SD) of total ADA activity (median, 71.4%; range, 25%-94%). Adenosine deaminase activity was significantly correlated with ADA2 activity ($r = 0.83; P = .000; n = 127$; Figure 2, top) and with IFN-γ level ($r = 0.30; P = .005; n = 82$; Figure 2, bottom).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.</th>
<th>Mean ± SD</th>
<th>Median</th>
<th>SEM</th>
<th>Range</th>
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</thead>
<tbody>
<tr>
<td>Leukocyte count, cells/mm³</td>
<td>230</td>
<td>3708.7 ± 5356.1</td>
<td>2205</td>
<td>353.2</td>
<td>27-48 000</td>
</tr>
<tr>
<td>Lymphocytes, %</td>
<td>230</td>
<td>77.0 ± 19.9</td>
<td>80.5</td>
<td>1.3</td>
<td>2-100</td>
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<tr>
<td>Cholesterol, mmol/L</td>
<td>254</td>
<td>2.46 ± 1.01</td>
<td>2.37</td>
<td>0.06</td>
<td>0.28-12.10</td>
</tr>
<tr>
<td>Protein, g/L</td>
<td>254</td>
<td>50 ± 8</td>
<td>51</td>
<td>0.5</td>
<td>22-90</td>
</tr>
<tr>
<td>LDH, U/L</td>
<td>254</td>
<td>734.1 ± 1364.2</td>
<td>471</td>
<td>85.6</td>
<td>32-18 000</td>
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<tr>
<td>ADA, U/L</td>
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<td>122.1 ± 48.4</td>
<td>119</td>
<td>3</td>
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</tr>
<tr>
<td>IFN-γ, pg/mL</td>
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<td>1899.4 ± 4381.5</td>
<td>503</td>
<td>483.8</td>
<td>13-29536</td>
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</table>
| *LDH indicates lactate dehydrogenase; ADA, adenosine deaminase; ADA2, adenosine deaminase 2; and IFN-γ, interferon gamma.†To convert cholesterol from millimoles per liter to milligrams per deciliter, divide millimoles per liter by 0.02586.

Table 2 lists the microbiologic and histological findings. By the definition of the study group, in all patients at least 1 of these tests had a positive result. The joint sensitivity of the analyses of biopsy tissue samples was 91.5% (227 of 248 patients), and that of pleural fluid sample analyses was 36.6% (93 of 254 patients). The most frequent finding (198 [79.8%] of 248 patients) was the observation of caseating granulomas in biopsy tissue samples. Of the 48 patients in whom the lung was affected, 30 (62.5%) had positive Ziehl-Neelsen sputum stains and all had positive Lowenstein sputum cultures.

Results of the tuberculin skin test were positive in 169 (66.5%) of 254 patients.

**COMMENT**

In Spain, the pleura is affected in 23.3% of all patients with tuberculosis,23 and in our hospital, tuberculosis is the most common cause (25%) of pleural effusions among patients cared for in the pneumology and internal medicine services.4

Since early this century,26 it has been recognized that tuberculous pleurisy is a delayed hypersensitivity reaction rather than an infection of the pleura. Cultures of pleural tissue and fluid from patients with tuberculous pleurisy are often negative,27 and in guinea pigs and mice, intrapleural injection of PPD 3 to 5 weeks after priming with a suspension of dead bacilli causes an exudative pleural effusion within 12 to 48 hours,28,29 whereas no such effusion is induced in sensitized animals by administration of antilymphocyte serum.30 Once mycobacterial protein enters the pleural cavity, there occurs a series of insufficiently elucidated immunologic reactions that give rise to the effusion.31

Tuberculous pleurisy was once considered generally to be a primary form of tuberculosis because it usually occurred in children and young adults in whom tuberculin skin test results had only recently been positive.
rather than negative. In recent years, several authors have reported that mean patient age has gradually risen and that tuberculous pleurisy is becoming a predominantly reactivated form of tuberculosis, at least in industrialized nations. In this study, the mean (±SD) age at occurrence was 34.1 ± 18.1 years, which is similar to that in previous studies. Although this study was not designed to classify tuberculous pleurisy as primary or reactivated tuberculosis, the low mean patient age, together with the low association with pulmonary lesions, suggests that, in our region, tuberculous pleurisy is still a primary tuberculosis.

Patient age is also of great diagnostic importance because in young patients, the presence of a pleural exudate with a high ADA concentration and a majority of lymphocytes among its leukocytes is highly suggestive of tuberculosis to the extent that pleural biopsy may be superfluous. The diagnosis of tuberculous pleurisy in older patients is more problematic because of the higher incidence of clinically similar disorders, neoplastic effusions in particular.

The determination of ADA activity in pleural fluid samples is now recognized as obligatory for characterization of a pleural exudate given its utility for the diagnosis of TPE. In our region, this marker of tuberculous pleurisy has a sensitivity of 100% and a specificity of 95%. The diagnosis of tuberculous pleurisy in older patients is more problematic because of the higher incidence of clinically similar disorders, neoplastic effusions in particular.

In the first studies of IFN-γ in this role, its sensitivity and specificity for tuberculous pleurisy were both 100%. In an earlier study of this lymphokine, its sensitivity and specificity were 94.2% and 91.8%, respectively. Two studies have reported figures for high IFN-γ concentrations and 9 pleural effusions of other kinds having high IFN-γ concentrations; in this study, its sensitivity was even lower, 89% (73 of 82 patients). Other authors have also reported cases of low IFN-γ levels in TPEs and high concentrations in neoplastic effusions. Further research is necessary to clarify the cause of high IFN-γ levels in non-TPEs. The fact that in this study the 9 TPEs with subthreshold IFN-γ levels all affected less than one third of the hemithorax recalls reports of TPEs of small extent being associated with IFN-γ concentrations only slightly above the diagnostic threshold. It would seem that the production of lymphokines by sensitized CD4+ lymphocytes must be low in such cases. In this study, results of the Mantoux test were also negative in 5 of 9 patients with subthreshold IFN-γ levels.

Although the rises in ADA and IFN-γ levels in TPE have different origins (infected macrophages in the case of ADA and sensitized CD4+ cells in that of IFN-γ), in this study, although not in certain others, and IFN-γ were correlated. This, together with the fact that the IFN-γ level is much more expensive to determine than the ADA level, suggests that determination of the IFN-γ level is not justified for routine characterization of pleural effusions.

One of our patients, aged 58 years, had an ADA concentration of only 22 U/L on first determination; but, on redetermination in a second sample, this figure rose to 62 U/L. Similar behavior was reported by Querol et al: of 9 patients with tuberculous pleurisy with subthreshold ADA concentrations on first determination, 5 had high levels on second determination.

Adenosine deaminase comprises 2 isoenzymes: ADA, which is found in all cells, and ADA2, which is found only in monocytes and macrophages. That the high ADA activity in patients with TPE is largely caused by ADA2 is corroborated by our findings that ADA2 contributed 72.2% ± 12.5% (mean ± SD) of total ADA activity in the 127 effusions in which it was determined, and that ADA and ADA2 were significantly correlated (r = 0.83; P = .000); this high ADA2 activity is caused by increased production by monocytes and macrophages that have been stimulated by live phagocytosed microorganisms. Our results also confirm previous findings in showing that ADA2, like total ADA activity, is a sensitive marker of tuberculous pleurisy, with 96.8% (123/127) of the effusions in this study having ADA2 concentrations higher than the diagnostic threshold of 40 U/L.

Interferon gamma is a lymphokine released by sensitized CD4+ lymphocytes. It increases the mycobactericidal activity of macrophages and has proved to be a useful marker for diagnosis of tuberculosis pleurisy. In the first studies of IFN-γ in this role, its sensitivity and specificity for tuberculous pleurisy were both 100%. In an earlier study of this lymphokine, its sensitivity and specificity were 94.2% and 91.8%, respectively. Two studies have reported low IFN-γ concentrations and 9 pleural effusions of other kinds having high IFN-γ concentrations; in this study, its sensitivity was even lower, 89% (73 of 82 patients). Other authors have also reported cases of low IFN-γ levels in TPEs and high concentrations in neoplastic effusions. Further research is necessary to clarify the cause of high IFN-γ levels in non-TPEs. The fact that in this study the 9 TPEs with subthreshold IFN-γ levels all affected less than one third of the hemithorax recalls reports of TPEs of small extent being associated with IFN-γ concentrations only slightly above the diagnostic threshold. It would seem that the production of lymphokines by sensitized CD4+ lymphocytes must be low in such cases. In this study, results of the Mantoux test were also negative in 5 of 9 patients with subthreshold IFN-γ levels.

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The sensitivities of the methods used for definitive diagnosis were similar to those reported in earlier studies. In particular, the joint sensitivity of the methods requiring pleural biopsy was 91.5%, similar to previously reported figures, caseating granulomas were observed in 79.8% (198/248) of patients, but Lowen-
stein culture allowed diagnosis in a further 29 patients. Thus, in general, pleural biopsy is the procedure affording the best chance of diagnosis.45

Results of the tuberculosis skin test were negative in 33.5% (85/254) of patients. Although similar results have been published previously,42 this is nevertheless a significant finding because the response to PPD in the dermis is mediated, as in the pleura, by interleukin 2 and IFN-γ (both produced by CD4+ cells), and IFN-γ levels were generally high in the pleural fluid of our patients. In 1 study,47 the response of circulating T cells to tuberculin was stifled by adherent suppressor cells. Negative skin test results can also be caused by the sequestration of helper and suppressor T cells in the pleural cavity.48

To sum up, we conclude that in our region, (1) the mean age of patients with tuberculous pleurisy is still low (<35 years); (2) there is no tendency for TPE to occur preferentially on either the right or the left side, and bilateral effusions are rare; (3) only about one fifth of patients suffer massive effusions; (4) the effusions have the biochemical characteristics of exudates and a majority of their leukocytes are lymphocytes; (5) ADA is a highly sensitive diagnostic marker of TPE because of increased ADA activity, with which it correlates well; (6) the most sensitive diagnostic criterion was the observation of caseating granulomas in biopsy tissue samples, but the joint sensitivity of this criterion and that of positive Lowenstein cultures was significantly higher; (7) a negative tuberculin skin test result does not rule out tuberculous pleurisy; and (8) the low mean age of patients, low radiological prevalence of pulmonary infiltrates, and high proportion of negative tuberculin skin test results suggest that tuberculous pleurisy is still a primary form of tuberculosis.

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REFERENCES