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 ADA 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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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 stains and Lowenstein cultures of pleural fluid; and tuberculin skin tests. In addition, the cytologic features of pleural fluid (total leukocyte count and percentage of lymphocytes) were determined in 230 patients; pleural fluid ADA2 and IFN-γ levels were determined in 127 and 82 patients, respectively; pleural biopsy tissue samples were investigated 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.

Pleural effusions were deemed slight if they affected less than one third of the hemithorax, moderate if they affected between one third and two thirds of the hemithorax, and massive if they affected more than two thirds of the hemithorax. Protein (in grams per liter), lactate dehydrogenase (in units per liter), and cholesterol (in millimoles per liter [milligrams per deciliter]) levels were determined by methods described elsewhere, as was IFN-γ level (in picograms per milliliter). Adenosine deaminase activity (in units per liter) was determined by the Giusti method, and ADA activity (in units per liter) was calculated from the activities of ADA and 2'-deoxyadenosine deaminase and the known affinities of ADA for adenosine and 2'-deoxyadenosine. Thoracocentesis was performed as usual and, except in patients in whom macroscopic findings suggested empyema, was followed by pleural biopsy with Cope or Abrams needles. Tuberculin skin tests were effected by intradermal injection of 0.1 mL of PPD containing 2 units of PPD RT-23; tests were read 48 to 72 hours later, and results were deemed positive if an induration of 5 mm or more in diameter was observed. No other tests for anergy were performed.

Results were analyzed statistically after previous verification that continuous variables were normally distributed. Interferon gamma concentrations were subjected to logarithmic transformation to normalize their distribution. Correlations were quantified by means of the Pearson correlation coefficient. Differences were considered significant at $P<.05$ in all statistical tests. The values of the biochemical markers that were used as diagnostic thresholds were those identified as optimal for this purpose in previous studies.

In this article, we review all the case histories of patients with TPE who have been diagnosed with certainty in our center during the past 8 years. Our aim was to determine (1) the age at which the effusion occurs, (2) the most common radiological signs, (3) the biochemical characteristics of the effusion, (4) the sensitivities of the various diagnostic tests, and (5) the utility of certain combinations of clinical, radiological, and analytic data for diagnosis.

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 ADA 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 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 tuberculosis skin test results had only recently been positive.

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**Table 1. Cytologic and Biochemical Characteristics of Tuberculous Pleural Effusions: Descriptive Statistics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.</th>
<th>Mean ± SD</th>
<th>Median</th>
<th>SEM</th>
<th>Range</th>
</tr>
</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>
</tr>
<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>
</tr>
<tr>
<td>ADA, U/L</td>
<td>254</td>
<td>122.1 ± 48.4</td>
<td>119</td>
<td>3</td>
<td>22-435</td>
</tr>
<tr>
<td>ADA2, U/L</td>
<td>127</td>
<td>90.0 ± 27.5</td>
<td>92</td>
<td>2.4</td>
<td>16-166</td>
</tr>
<tr>
<td>IFN-γ, pg/mL</td>
<td>82</td>
<td>1899.4 ± 4381.5</td>
<td>503</td>
<td>483.8</td>
<td>13-29 536</td>
</tr>
</tbody>
</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.

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**Table 2. Sensitivity of Each of the Criteria Used for Definitive Diagnosis of Tuberculous Pleurisy**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ziehl-Neelsen staining of pleural fluid</td>
<td>14/254 (5.5)</td>
</tr>
<tr>
<td>Culture of pleural fluid in Lowenstein medium</td>
<td>93/254 (36.6)</td>
</tr>
<tr>
<td>Ziehl-Neelsen staining of biopsy tissue</td>
<td>64/248 (25.8)</td>
</tr>
<tr>
<td>Culture of biopsy tissue in Lowenstein medium</td>
<td>140/248 (56.4)</td>
</tr>
<tr>
<td>Observation of caseating granulomas</td>
<td>198/248 (79.8)</td>
</tr>
<tr>
<td>Ziehl-Neelsen staining of sputum</td>
<td>30/48 (62.5)</td>
</tr>
<tr>
<td>Culture of sputum in Lowenstein medium</td>
<td>48/48 (100.0)</td>
</tr>
</tbody>
</table>

Figure 1. Age distribution of patients with tuberculous pleural effusion.

Figure 2. Correlation between adenosine deaminase (ADA) and ADA2 (top) and interferon gamma (IFN-γ) (bottom).
rather than negative. In recent years, several authors reported that mean patient age has gradually risen\(^3\) 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.\(^1\) 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 makes pleural biopsy unnecessary if the patient is young (<35 years). This is partly because of the high prevalence of tuberculous pleuritis in this region, which increases the positive predictive value and efficiency of ADA concentration as a diagnostic marker (Figure 3).\(^9\) In other regions, the efficiency of this marker will not necessarily be as high, and clinicians are accordingly advised to determine this variable for their own region.\(^3\)

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\(^3\): 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\(_1\), which is found in all cells, and ADA\(_2\), which is found only in monocytes and macrophages.\(^3\) That the high ADA activity in patients with TPE is largely caused by ADA\(_2\) is corroborated by our findings that ADA\(_2\) contributed 72.2% ± 12.5% (mean ± SD) of total ADA activity in the 127 effusions in which it was determined, and that ADA and ADA\(_2\) were significantly correlated (\(r = 0.83\); \(P = .000\)); this high ADA\(_2\) activity is caused by increased production by monocytes and macrophages that have been stimulated by live phagocytosed microorganisms.\(^3\) Our results also confirm previous findings\(^3\) in showing that ADA\(_2\) is a sensitive marker of tuberculous pleurisy, with 96.8% (123/127) of the effusions in this study having ADA\(_2\) 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 tuberculous pleurisy.\(^9\) In the first studies of IFN-\(\gamma\) in this role,\(^3\) its sensitivity and specificity for tuberculous pleurisy were both 100%. In an earlier study\(^9\) of this lymphokine, its sensitivity and specificity were 94.2% and 91.8%, respectively, 2 TPEs having low IFN-\(\gamma\) concentrations and 9 pleural effusions of other kinds having high IFN-\(\gamma\) concentrations; in this study, its sensitivity was even lower, 89% (73 of 82 patients). Other authors also reported cases of low IFN-\(\gamma\) levels in TPEs\(^4\) and high concentrations in neoplastic effusions,\(^4\) parapneumonic effusions,\(^4\) and non-TPEs of unknown cause.\(^4\) Further research is necessary to clarify the cause of high IFN-\(\gamma\) levels in non-TPEs. The fact that in this study the 9 TPEs with subthreshold IFN-\(\gamma\) levels all affected less than one third of the hemithorax recalls reports of TPEs of small extent being associated with IFN-\(\gamma\) concentrations only slightly above the diagnostic threshold.\(^9\) 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-\(\gamma\) levels.

Although the rises in ADA and IFN-\(\gamma\) levels in TPE have different origins (infected macrophages in the case of ADA and sensitized CD4\(^+\) cells in that of IFN-\(\gamma\)), in this study, although not in certain others,\(^9\) ADA and IFN-\(\gamma\) were correlated. This, together with the fact that the IFN-\(\gamma\) level is much more expensive to determine than the ADA level, suggests that determination of the IFN-\(\gamma\) level is not justified for routine characterization of pleural effusions.

The sensitivities of the methods used for definitive diagnosis were similar to those reported in earlier studies.\(^7\) In particular, the joint sensitivity of the methods requiring pleural biopsy was 91.5%, similar to previously reported figures,\(^4\) casating 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.

Results of the tuberculin skin test were negative in 33.5% (85/254) of patients. Although similar results have been published previously,27 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 ADA2 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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