The Relationship between Pleural Fluid Findings and the Development of Pleural Thickening in Patients with Pleural Tuberculosis*

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The objective of the study was to determine if residual pleural thickening after treatment for pleural tuberculosis could be predicted from the pleural fluid findings at the time of the initial thoracentesis. Forty-four patients initially diagnosed as having pleural tuberculosis between January 1986 and January 1988 were separated into two groups: the 23 patients in group 1 had residual pleural disease, while the 21 patients in group 2 had no residual pleural disease after treatment for their pleural tuberculosis was completed. The clinical characteristics of the two different groups did not differ significantly, but the patients in group 1 tended to be a little sicker in that the duration of their symptoms was longer, their hemoglobin values were lower, and weight loss and cough were more frequent. There were no significant differences in the pleural fluid findings in the two different groups. The mean pleural fluid protein level was 5.40 ± 0.58 g/dl for group 1 and 5.17 ± 0.80 g/dl for group 2, while the mean pleural fluid glucose level was 78.6 ± 19.5 mg/dl for group 1 and 79.5 ± 20.1 mg/dl for group 2. The mean pleural fluid lactate dehydrogenase (LDH) level in group 1 was 593 ± 496 IU/L, while the mean level for group 2 was 491 ± 196 IU/L. The presence of residual pleural thickening was not related to the chemotherapeutic regimen or the performance of a therapeutic thoracentesis. From this study we conclude that approximately 50 percent of patients with pleural tuberculosis will have residual pleural thickening when their therapy is completed, but that one cannot predict which patients will have residual pleural thickening from either their clinical characteristics or their pleural fluid findings.

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As sizable a percentage of patients who have pleural tuberculosis have residual pleural thickening after treatment for the tuberculosis is completed.1,2 The incidence of residual pleural thickening appears to be largely independent of the treatment,1,2 although one report suggests that the administration of corticosteroids decreases the incidence of residual pleural thickening2 and another suggests that a therapeutic thoracentesis decreases the incidence of residual pleural thickening.3

We hypothesized that those patients who had the highest amount of pleural inflammation as evidenced by the highest levels of lactate dehydrogenase (LDH) and the lowest levels of glucose in the pleural fluid would be those most likely to develop residual pleural thickening. In this retrospective study of 44 patients, the occurrence of residual pleural thickening was correlated with the pleural fluid findings at the time of the initial thoracentesis.

MATERIALS AND METHODS

Between January 1986 and January 1988, 71 patients with pleural tuberculosis were seen at the Hospital das Clinicas of the Faculty of Medicine of the University of Sao Paulo (Brazil). All patients who had either a pleural biopsy specimen showing granulomas with caseous necrosis and/or pleural fluid or pleural tissue positive on culture for Mycobacterium tuberculosis were included in the study. Forty-four patients returned to follow-up after 6 to 12 months and these patients form the study population.

Prior to treatment, the following data were obtained: patient's age; duration of symptoms; presence or absence of fever, weight loss, chest pain, night sweats, dyspnea, and cough; reaction to intradermal purified protein derivative (PPD); level of protein, glucose, LDH, and amylase in the pleural fluid; level of protein, glucose, and LDH in the serum; cellular composition of the pleural fluid; and the size of the effusion. The effusion was classified as large if on the posteroanterior chest roentgenogram the effusion occupied more than one third the distance between the lateral chest wall and the mediastinum at the level of the hilar region.4 In addition, the histologic features and culture results of the pleural biopsy specimen and the culture results of the pleural fluid were recorded.

During the study period, several different treatment regimens for pleural tuberculosis were used. Fourteen patients received isoniazid, rifampin, and pyrazinamide for the initial two months followed by an additional seven months of therapy with isoniazid and rifampin. Twelve patients received isoniazid and rifampin for nine months and an additional 12 patients received isoniazid, rifampin and pyrazinamide for the initial two months followed by four additional months of isoniazid and rifampin therapy. Four patients received rifampin, ethambutol, and isoniazid for three months, ethambutol and isoniazid for another three months, and isoniazid alone for an additional three months. Two patients received other regimens. Eleven patients underwent therapeutic thoracentesis of more than 500 ml. No patient received corticosteroids.
Table 1—Comparison of Clinical Characteristics in Patients with Residual Pleural Thickening (Group 1) and Those without Pleural Thickening (Group 2)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1, No. (%)</th>
<th>Group 2, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr, mean ± SD</td>
<td>35.8 ± 13.1</td>
<td>34.8 ± 14.3</td>
</tr>
<tr>
<td>Hemoglobin, g/dl</td>
<td>12.1 ± 1.9</td>
<td>12.4 ± 1.2</td>
</tr>
<tr>
<td>Duration of symptoms, ≥8 wk*</td>
<td>6/14 (43)</td>
<td>2/10 (20)</td>
</tr>
<tr>
<td>Fever</td>
<td>21/23 (91)</td>
<td>20/21 (95)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>19/23 (83)</td>
<td>15/21 (71)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>21/23 (91)</td>
<td>20/21 (95)</td>
</tr>
<tr>
<td>Night sweats</td>
<td>12/23 (52)</td>
<td>11/21 (52)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>15/23 (65)</td>
<td>13/21 (62)</td>
</tr>
<tr>
<td>Cough</td>
<td>16/23 (70)</td>
<td>12/21 (57)</td>
</tr>
</tbody>
</table>

*Data unavailable for nine patients in group 1 and 11 patients in group 2.

The 44 patients were separated into two groups based on their chest roentgenograms at the end of treatment (6 to 12 months after the diagnosis depending on the therapeutic regimen). The 23 patients in group 1 had residual pleural thickening that was defined as a pleural thickening greater than 2 mm on the lateral-inferior portion of the posteroanterior chest roentgenogram. The 21 patients in group 2 had no such thickening.

Statistical Analysis

The data are expressed as the mean ± the standard deviation unless otherwise noted. The pleural fluid protein, LDH, and glucose levels and the ratio of the pleural fluid to serum protein, LDH, and glucose levels in the 23 patients with residual pleural thickening and the 21 patients without residual pleural thickening were compared with the unpaired t test. The percentage of patients with various clinical characteristics or receiving different treatment regimens in the two different groups were compared with the χ² test.

RESULTS

The clinical characteristics of the 23 patients with and the 21 patients without residual pleural thickening were quite similar (Table 1). The mean ages and hemoglobin levels were nearly identical in the two groups. There was no significant difference in the fraction of patients with fever, weight loss, chest pain, night sweats, dyspnea, or cough in the two different groups, although the group that was left with residual thickening did have a slightly longer duration of symptoms and slightly higher incidence of weight loss and cough. Although more than 50 percent of the study population had residual pleural thickening at the last follow-up visit, the pleural thickening itself did not appear to be responsible for symptoms at this visit in any of the patients.

The skin test results, roentgenographic findings, and pleural biopsy and culture results did not differ significantly between the two different groups (Table 2). The patients with residual pleural thickening tended to have a higher incidence of a PPD with greater than 15 mm induration and tended to have a higher incidence of large pleural effusions, but they tended to have a lower incidence of positive pleural fluid cultures and a lower incidence of positive acid-fast bacilli (AFB) smears. The patients whose final evaluation occurred after six months of therapy had no higher incidence of pleural thickening than did those whose evaluation occurred after nine or more months of therapy. Likewise, the incidence of residual pleural thickening did not appear to be related to the chemotherapeutic regimen or whether the patient had received a therapeutic thoracentesis.

There appeared to be no relationship between residual pleural thickening and the level of protein, glucose, or LDH in the pleural fluid at the time of the initial thoracentesis. The mean protein and LDH

**Figure 1. Levels of pleural fluid protein in patients with and without residual pleural thickening.**
levels were slightly higher while the mean pleural fluid glucose level was slightly lower in patients with residual pleural effusions. The distribution of the values for the pleural fluid levels of protein (Fig 1), glucose (Fig 2) and LDH (Fig 3) were virtually identical in the two different groups.

The mean ratio of the pleural fluid to serum protein level was similar in the group with thickening (0.72 ± 0.08) and the group without thickening (0.72 ± 0.10). Likewise, the ratio of the pleural fluid to serum glucose and LDH were similar in the groups with thickening (0.76 ± 0.25 and 2.58 ± 1.70, respectively) and without thickening (0.85 ± 0.17 and 2.74 ± 1.33, respectively).

The data were also analyzed to determine if there was a significant relationship between the levels of glucose and LDH in the pleural fluid of the entire group of patients. There was a significant relationship between the ratio of the pleural fluid to serum glucose and the ratio of the pleural fluid to serum LDH (r = −0.51, p<0.01). The minus sign on the correlation coefficient indicates that low glucose levels are associated with high LDH levels. There were no significant correlations among the absolute levels of protein, glucose, and LDH in the pleural fluid.

**Discussion**

The present study demonstrates that there is approximately a 50 percent incidence of residual pleural thickening when chemotherapy is completed for pleural tuberculosis. The incidence of residual thickening does not appear to be related to the initial biochemical findings in the pleural fluid or the clinical characteristics of the patients at the time of presentation. Moreover, the incidence of residual thickening was not related to the chemotherapeutic regimen or the performance of a therapeutic thoracentesis. In one previous report, patients who had undergone therapeutic thoracentesis had a significantly lower incidence of residual pleural thickening.

We had hypothesized that those individuals who had lower pleural fluid glucose levels or higher pleural fluid LDH levels would be more likely to have residual pleural thickening. The level of pleural fluid LDH is thought to be correlated with the degree of pleural inflammation. Certainly in patients with parapneumonic effusions, the lower the pleural fluid glucose level or the higher the pleural fluid LDH level, the more likely that the patient is to require chest tubes. Furthermore, a low pleural fluid glucose level in patients with malignant pleural effusions is associated with a large tumor burden. However, the data from our study offered no support for our hypothesis.

In the present study, there was no relationship between the treatment that the patient received and residual pleural thickening. When one reviews the natural history of untreated tuberculous pleuritis, one
should not be surprised at this finding. Roper and Waring followed 141 individuals who had exudative pleuritis and a positive skin test to PPD. The patients, who were first diagnosed in 1944 or 1945, were treated only with bed rest. At the end of their initial hospitalization, only 48 (34 percent) had more than slight residual pleural thickening. Since residual pleural disease from tuberculosis tends to improve with time, we thought that those patients who were evaluated after six months of therapy might have a higher incidence of residual pleural thickening than those evaluated after nine months of therapy, but this was not the case in the present study (Table 2).

If the residual pleural disease is related neither to the initial biochemical findings nor to the treatment, what is it related to? The patients with residual thickening tended to have a larger PPD, a lower incidence of positive pleural fluid cultures, and a lower incidence of positive AFB smears. These observations suggest that delayed hypersensitivity rather than the inflammatory response to infection is responsible for the fibrosis. The local inflammatory hypersensitivity response with tuberculous pleuritis is mediated in part by a number of inflammatory and immunostimulatory factors, including complement degradation products, interferon gamma, and interleukin 1.

Since it is becoming increasingly clear that cytokines modulate the development of fibrosis, one might anticipate that there would be some relationship between the level of hypersensitivity and the development of pleural fibrosis.

We had also anticipated that there would be a significant negative correlation between the levels of LDH and the levels of glucose in the pleural fluid. This has been the case with parapneumonic and malignant pleural effusions. In the present study, there was not a significant correlation between the levels of glucose and LDH in the pleural fluid, although there was a significant relationship between the ratios of the pleural fluid to the serum LDH and glucose. The lack of a significant correlation with the absolute levels was quite possibly related to the relatively narrow range of pleural fluid glucose levels.

In conclusion, the results of the present study fail to support our hypothesis that residual pleural thickening would be more common in patients with pleural tuberculosis with a higher degree of pleural inflammation as evidenced by lower pleural fluid glucose levels and higher pleural fluid LDH levels. The incidence of residual pleural thickening was slightly above 50 percent, but the presence of the residual pleural thickening was not associated with clinical symptoms. It is unlikely that the mild degrees of residual thickening observed in the present study have any clinical significance. Although documentation of the changes in pulmonary function with residual pleural thickening were not documented in this or in previous studies, patients with asbestososis and much greater amounts of pleural thickening have only mild reductions in their pulmonary function test results.

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