Resolution of Residual Pleural Disease According to Time Course in Tuberculous Pleurisy During and After the Termination of Antituberculosis Medication*

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Study objectives: To assess the resolution of pleural disease in patients with tuberculous pleurisy (TP) during and after antituberculosis medication.

Design: An observational, prospective, longitudinal study.


Patients and methods: Chest radiographs of 85 adult TP patients were followed up prospectively from diagnosis to 24 months after the start of medication. The extent of pleural disease, synonymous with the radiographic term, pleural opacity (PO), was evaluated at regular intervals according to a size scale. Additionally, following completion of 6 months of therapy, residual PO (RPO) was determined by either measurement of the widest width of the opacity, if loculated, or at the superior level of the hemidiaphragm.

Results: Seventy-seven patients had a PO graded ≥ 2 at the initial presentation. At 6, 9, and 24 months, the number of patients with these grades declined. At these time periods, there were 14, 8, and 7 patients, respectively, remaining with this classification. RPO > 10 mm at 24 months was considered indicative of significant residual pleural disease. During the period after 6 months of antituberculosis medication, the number of patients with RPO ≥ 10 mm declined from 43 patients at 6 months to 21 patients at 24 months. The presence of loculation on an initial chest decubitus view was associated with significant RPO at 24 months (p = 0.009).

Conclusion: In TP patients, improvement of RPO often occurred even after completion of 6 months of antituberculosis medication up to 24 months. A loculated PO at initial presentation, but not initial PO size, was a predictor of significant RPO at 24 months.

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Key words: pleural effusion; pleural thickening; tuberculosis

Abbreviations: ADA = adenosine deaminase; AFB = acid-fast bacilli; ESR = erythrocyte sedimentation rate; LDH = lactate dehydrogenase; PO = pleural opacity; RPO = residual pleural opacity; RPT = residual pleural thickening; TP = tuberculous pleurisy

Tuberculous pleurisy (TP) is a common cause of exudative pleural effusion. Before therapy was standardized, several studies1–3 administered different drug regimens and reported resolution of effusion from 3 to 9 months, with the majority of clearing at 3 to 6 months. The current recommendation for TP consists of isoniazid, rifampin, and pyrazinamide for 2 months, followed by isoniazid and rifampin for 4 months.4 Using this standard regimen, excellent treatment results have been reported in terms of relieving symptoms and preventing pulmonary tuberculosis recurrence.5,6 However, despite this therapeutic success, many studies7–10 have also reported residual pleural thickening (RPT) after treatment in

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a significant proportion of patients. The majority of studies on this topic measured RPT at medication termination. However, several reports have mentioned further resolution of RPT after treatment discontinuation. We have experienced sporadic cases of TP patients that have shown residual pleural disease improvements long after treatment. Thus, we undertook this study to determine the frequency and the period over which such delayed improvement occurs in TP patients, and to identify the circumstances that are lead to such a phenomenon by prospectively following up chest radiographs.

**Materials and Methods**

**Study Population**

The study population comprised of HIV-negative TP patients ≥ 16 years old who were admitted to Seoul National University Boramae Hospital for the evaluation of pleural effusion between December 1998 and June 2001. All patients underwent diagnostic thoracentesis, and pleural fluid cell count, differential count, biochemistry including lactate dehydrogenase (LDH), glucose, proteins, and microbiology and adenosine deaminase (ADA) levels were studied. The diagnosis of TP was made if there were at least one of following criteria: (1) the detection of *Mycobacterium tuberculosis* in pleural fluid by acid-fast bacilli (AFB) smear and/or culture; (2) typical histologic findings of a pleural biopsy specimen; (3) the presence of active pulmonary tuberculosis; and (4) typical clinical and pleural fluid findings that could exclude other causes (lymphocyte dominant and an ADA level > 60 IU/L) in cases without bacteriologic or histologic confirmation. Active pulmonary tuberculosis was diagnosed if there was at least one of following criteria: (1) positive AFB smear and/or culture findings for *M tuberculosis* in sputum or bronchial washing fluid; (2) histologic confirmation of biopsy specimen of the lung lesion; and (3) chest radiographic findings compatible to tuberculosis with a favorable response to treatment in cases without bacteriologic or histologic confirmation.

During the study period, 130 consecutive patients received a diagnosis and were treated for TP. Subjects were treated initially with the following daily regimen: isoniazid, 400 mg (300 mg for patients with < 50 kg of body weight); rifampicin, 600 mg (450 mg for patients with < 50 kg of body weight); ethambutol, 800 mg (600 mg for patients with < 50 kg of body weight); and pyrazinamide, 1,500 mg (1,000 mg for patients with < 50 kg of body weight). All patients were seen by a physician 1 week after the start of medication and monthly thereafter, and at these visits they were questioned about drug compliance and side effects. Treatment duration was 9 months, except for four patients who received medication for 6 months. Patients who complained of dyspnea due to large pleural effusions underwent one or two therapeutic thoracentesis procedures in order to relieve the symptoms after diagnostic thoracentesis. Except for the initial therapeutic thoracentesis to relieve dyspnea in some patients during hospital admission, no other measures such as steroids, follow-up thoracentesis, or drainage procedure were performed during the treatment period. Our institutional review board approved our research study and did not require patient informed consent. We obtained written informed consent from all patients to perform the thoracentesis.

**Radiologic Analysis**

Although some patients underwent CT scan as well as lateral or decubitus radiography, only chest posteroanterior radiographs were analyzed during the study. Since previous studies and our personal experiences indicate that interval changes of pleural disease tend to be dramatic during the first few months of treatment, and then become subtle, we decided to assess the severity of pleural disease in two different ways: pleural opacity (PO) for pleural disease observed initially, and then residual PO (RPO) for pleural disease observed after 6 months of antituberculosis medication. For assessment of PO size, we modified a scaling system used by Wait et al as follows. 1 = costophrenic angle obscured; 2 = entire diaphragm obscured; 3 = entire diaphragm obscured, but fluid level below the hilum; 4 = up to the hilum; and 5 = above the hilum. The assessment of PO was done at disease presentation and after 3 months and 6 months of therapy. In addition, we performed the same qualitative assessment of PO at 9, 12, and 24 months, so as allow interval changes in PO to be followed throughout the study period.

To quantitatively assess RPO after 6 months of antituberculosis medication, we measured the distance from the lateral chest wall to the innermost margin of the opacity at the level of the highest point of the hemidiaphragm. However, in some patients, interval changes of pleural disease were not readily assessable at the level of the hemidiaphragm. Typically, laterally formed loculations were present in these patients, which changed significantly in size with time. In these patients, the maximal horizontal thickness of a lateral loculation was measured instead. Assessments were done at 6, 9, 12, and 24 months in all patients, and continuous resolution of RPO was defined as at least 1 mm of reduction at every time point (6, 9, 12, and 24 months). Significant RPO was defined at ≥ 10 mm. After assessing POs using both methods, we investigated whether the initial PO was related to the subsequent development of significant RPO.

**Statistical Analysis**

Statistical analysis was performed using statistical software (SPSS version 11.0; SPSS; Chicago, IL). Data are expressed as means ± SD. Statistical differences were determined using the $t^2$ test with the Yates correction, but when sample numbers were < 5 the Fisher Exact Test was used. Student $t$ test and the paired $t$ test were used to compare means. The relationship between initial pleural fluid amount (initial grade) and RPO at 24 months was analyzed using the Kruskal-Wallis test. Linear regression analysis was performed to evaluate the association between RPO at 6 months and 24 months. All of these statistical studies were supported by the Medical Research Collaborating Center of Seoul National University Hospital.

**Results**

**Study Population**

During the study period, 130 consecutive TP patients were enrolled. After diagnostic workup for pleural effusion was finished, 25 patients returned to their local community hospital from where they were referred. Thirteen patients were not available for follow-up. Seven patients received decortication during antituberculosis medication and were excluded from the study population. Finally, 85 patients (54 men [57%] and 31 women; mean age, 39.2 ± 17.5
years; age range, 16 to 79 years) of the original 130 patients completed the antituberculosis medication and attended planned regular chest posteroanterior radiograph follow-ups for 24 months after treatment initiation and were included in this study. Coexistent pulmonary tuberculosis was found in 41 of the 85 patients (48.2%).

**Qualitative Assessment of PO**

PO size at the initial presentation of the study population was grade 1 in 8 patients, grade 2 in 24 patients, grade 3 in 10 patients, grade 4 in 28 patients, and grade 5 in 15 patients. Bilateral PO was observed in 3 patients, was right sided in 50 patients, and was left sided in 32 patients. PO tended to decrease continuously with medication, and the number of patients with grade 2 to grade 5 PO decreased from an initial 77 patients (90.6%) to 37 patients (43.5%) at 3 months, 14 patients (16.5%) at 6 months, 8 patients (9.4%) at 9 months, and 7 patients (8.2%) at 12 months and 24 months (Fig 1). There were no cases of tuberculous empyema or paradoxical worsening of effusion.

**Quantitative Assessment of RPO**

RPO was measured at time intervals after completion of treatment. The number of patients with RPO ≥ 10 mm decreased from 43 patients (50.6%) at 6 months, to 33 patients (38.8%) at 9 months, to 23 patients (27.1%) at 12 months, and to 21 patients (24.7%) at 24 months (Fig 1). Only two patients showed a reduction of significant RPO between 12 months and 24 months. Their RPOs at 12 months were 10 mm in both patients. No significant relationship was found between RPO at 24 months and the initial PO size (Fig 2).

The number of patients with RPO ≥ 10 mm 6 months decreased at 12 months and 24 months, but neither were associated with initial PO size (Fig 3).

RPO at 24 months was associated with RPO at 6 months (Fig 4) \( [r = 0.786, p < 0.01] \). No patients with RPO ≥ 60 mm at 6 months reached < 10 mm at 24 months. RPO ≥ 10 mm at 24 months was only correlated with loculation of pleural fluid in the initial chest decubitus view (Table 1) and was not correlated with any other parameters, eg, pleural fluid LDH or protein level. Mean RPO decreased continuously (Fig 5), with a mean RPO of 17.9 ± 20.5 mm at 6 months, 12.3 ± 16.4 mm at 9 months, 10.3 ± 15.6 mm at 12 months, and 8.8 ± 15.8 mm at 24 month. In 49 of the 85 patients (57.6%), RPO decreased by at least 1 mm between 6 months and 24 months. The range of resolution after 6 months of treatment to 24 months was from 0 to 47 mm (Fig 6). The amount of resolution after 6 months of medication was < 10 mm in 20 patients, ≥ 10 mm but < 20 mm in 13 patients, ≥ 20 mm but < 30 mm in 7 patients, ≥ 30 mm but < 40 mm in 5 patients, and ≥ 40 mm in 4 patients. The 49 patients who showed further resolution after 6 months of antitu-

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**Figure 1.** Interval improvement of both PO and RPO during and after antituberculosis medication.

**Figure 2.** RPO at 24 months after antituberculosis medication commencement according to initial PO size.

**Figure 3.** The number of patients with significant RPO (≥ 10 mm) at 6, 12, and 24 months after treatment commencement according to the initial size of PO.
Bacterial medication had significantly higher erythrocyte sedimentation rate (ESR) and pleural fluid LDH levels on initial presentation than other patients (Table 2). No other pleural fluid constituents such as protein, glucose, ADA, or clinical parameters such as age, sex, and symptom duration were found to be significantly related with the resolution of RPO after treatment. Three of the 49 patients who showed continuous resolution received 6 months of antituberculosis medication, and the others received 9 months of treatment. The presence of pulmonary tuberculosis or loculation on the initial chest decubitus view also showed no significant relation with this further resolution.

**Table 1—General Clinical and Pleural Fluid Parameters of Patients With TP With RPOs ≥ 10 mm or < 10 mm at 24 mo After Antituberculosis Treatment**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>RPO at 24 mo</th>
<th>p</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥ 10 mm</td>
<td>&lt; 10 mm</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>43.1 ± 19.0</td>
<td>37.9 ± 16.9</td>
<td>NS</td>
</tr>
<tr>
<td>Male/female gender</td>
<td>15/6</td>
<td>39/25</td>
<td>NS</td>
</tr>
<tr>
<td>Symptom duration, wk</td>
<td>3.3 ± 2.5</td>
<td>3.4 ± 4.6</td>
<td>NS</td>
</tr>
<tr>
<td>Pulmonary tuberculosis</td>
<td>15</td>
<td>28</td>
<td>NS</td>
</tr>
<tr>
<td>Sputum AFB</td>
<td>5</td>
<td>13</td>
<td>NS</td>
</tr>
<tr>
<td>Pleural AFB</td>
<td>13</td>
<td>16</td>
<td>NS</td>
</tr>
<tr>
<td>Initial loculation</td>
<td>13</td>
<td>20</td>
<td>0.009</td>
</tr>
<tr>
<td>WBC count, cells/µL</td>
<td>6,156 ± 1,356</td>
<td>6,208 ± 1,470</td>
<td>NS</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>49.9 ± 30.5</td>
<td>43.4 ± 26.7</td>
<td>NS</td>
</tr>
<tr>
<td>Pleural fluid glucose, mg/dL</td>
<td>87.3 ± 31.2</td>
<td>97.9 ± 35.1</td>
<td>NS</td>
</tr>
<tr>
<td>Pleural fluid protein, mg/dL</td>
<td>5.923 ± 557</td>
<td>5.944 ± 552</td>
<td>NS</td>
</tr>
<tr>
<td>Pleural fluid LDH, U/L</td>
<td>537.6 ± 313.6</td>
<td>460.5 ± 260.3</td>
<td>NS</td>
</tr>
<tr>
<td>Pleural fluid ADA, IU/L</td>
<td>81.6 ± 37.1</td>
<td>81.9 ± 25.6</td>
<td>NS</td>
</tr>
<tr>
<td>Pleural fluid lymphocyte, %</td>
<td>76.2 ± 22.4</td>
<td>77.0 ± 20.5</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD or No. of patients; NS = not significant.

**Discussion**

Our study shows that radiographic improvement of TP occurs even after 6 months of antituberculosis chemotherapy. The number of patients with significant (≥10 mm) RPO decreased from 43 patients at 6 months to 21 patients at 24 months. The presence of loculation on the initial chest decubitus view, and not initial PO size, was associated with significant RPO at 24 months. Forty-nine of the 85 patients (57.6%) showed further resolution of RPO after 6 months of antituberculosis medication, and this phenomenon is associated with significantly higher levels of initial ESR and pleural fluid LDH but not with initial PO size. It was noteworthy that although mean RPO decreased from 10.3 ± 15.6 mm at 12 months to 8.8 ± 15.8 mm at 24 months, only two patients with significant RPO (10 mm in both patients) at 12 months showed reduction to < 10 mm at 24 months.

A small number of studies have described the natural course of TP after treatment. De Pablo et al.10 evaluated chest radiographs of 13 patients 1 year after treatment and found that RPT decreased by 3

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**Figure 4.** The relation between RPO at 6 months and 24 months after the start of antituberculosis treatment. There was strong positive correlation between two intervals (p < 0.01). No patients with an RPO ≥ 60 mm at 6 months reached < 10 mm at 24 months (vertical dotted line).

**Figure 5.** Reduction of RPO from 6 to 24 months after starting antituberculosis medication. Each reduction was significant (p < 0.05).

**Figure 6.** The range of reduction of RPO between 6 months and 24 months after the start of antituberculosis medication.
to 28 mm in 10 patients. Lee et al. performed a prospective, placebo-controlled study in 40 TP patients and showed radiographic evidence of lung field clearing that occurred >1 year after the start of antituberculosis medication in some patients. Galarza et al. reported that mean maximal pleural thickening in their TP patients was reduced at 12 months compared to that of 6 months, when medication was concluded in both placebo and steroid-use groups. All of these studies showed that further resolution of pleural disease occurs after the conclusion of antituberculosis medication in patients with TP. However, our study differed in that it was a prospective study of patients who were followed up at regular intervals extending to 24 months.

Our results also contrast with the current recommendation to wait for at least 6 months after treatment commencement before considering decortication. Combined with our finding that no patient with RPO ≥ 60 mm at 6 months achieved RPO < 10 mm at 24 months, it seems advisable to delay decortication until 12 months after treatment start if the RPO is < 60 mm at 6 months.

To describe radiographic shadows of TP, we used the terms pleural opacity for initial abnormality and residual pleural opacity for changes that occurred after standard 6 months of therapy. The reason why we used these terms instead of residual pleural thickening for a pleural disease was that we could not tell for sure whether such a pleural shadow represents an effusion or a thickening in those periods.

Investigations such as ultrasound, or CT scan were not done in our study. Indeed, our own study results can be described better using PO or RPO since radiographic improvement of “pleural effusion or thickening” may make the terms conflict.

In the present study, the relatively high levels of inflammatory markers (ESR and pleural fluid LDH) in patients who subsequently showed further resolution 6 months after start of treatment provide evidence that supports the inflammatory nature of TP at this stage of the disease. There have been several contradictory reports about pleural fluid parameters and pleural thickening in patients with TP. Barbosa et al. after analyzing the RPT and pleural fluid constituents in 44 TP patients, reported that one cannot predict which patients will have RPT from their pleural fluid findings such as protein, LDH, and glucose levels in TP. But, significantly lower glucose levels and pH and higher lysozyme and tumor necrosis factor-α levels was observed in the pleural fluid of patients with RPO ≥ 10 mm in the study by de Pablo et al. Our study differed from the previous studies in that ours involved a larger study population and compared RPO ≥ 10 mm at 24 months, not at the termination of medication. We presume that patients who show continuous resolution have relatively severe inflammation that requires more time to resolve. However, we offer no explanation as to why no differences were found in other inflammatory markers such as pleural fluid glucose or protein levels. It could be that these pleural fluid markers are not sensitive enough to predict the course of pleural inflammation.

The incidence of RPO after antituberculosis treatment varies by the study. In our study, RPO ≥ 10 mm was viewed as significant thickening because RPO of 10 mm is known to cause functional disturbances. Some authors have reported a high incidence of RPO ≥ 10 mm after treatment, whereas Candela et al. reported that only 6% of their study population had RPO in this range. In our study, 43 patients (50.6%) at 6 months and 33 patients (38.8%) at 9 months had RPO ≥ 10 mm, which is much higher than previously reported. We offer no satisfactory explanation for this higher incidence of significant RPO vs other reports and can only suspect that advanced age, the high prevalence of concurrent active pulmonary tuberculosis, and the relatively longer symptom duration of our subjects may have played roles. In addition, racial factors may also have contributed.

Our study has several limitations. First, we excluded seven patients who received decortication. These seven patients had grade 4 or grade 5 effusion initially and showed no gross change despite >3 months of antituberculosis medication. Thus, our
data may underestimate RPO at 24 months. Also, a bias in the prevalence of RPO may have been introduced by the initial exclusion of 25 patients transferred to other hospital or 13 patients unavailable for follow-up of the original 130 patients.

Second, it should be noted that although we started taking RPO measurements at 6 month after therapy commencement, unlike other studies, most of our study subjects received 9 months of antituberculosis medication. Although the standard 6-month regimen is known to have excellent results in terms of both resolution and relapse rate, it is also true that we do not know whether or not the observed improvement in our patients between 6 months and 9 months of treatment was entirely spontaneous.

Third, we did not explore the nature of the RPO. Since cross-sectional image modalities such as CT were not used, we could not establish whether RPO improvements were caused by effusion volume or solid inflammatory tissue reductions, or both. Moreover, we did not obtain samples from the RPO. The observation that reductions in inflammatory markers (ESR and pleural fluid LDH) from effusions obtained at disease presentation were higher in patients whose RPOs were reduced after 6 months suggests that inflammation was more severe in those patients. But we offer no explanation why no differences were observed in other inflammatory markers such as pleural fluid glucose or protein levels.

Fourth, we performed one or two therapeutic thoracenteses during the initial diagnostic period in dyspneic patients with a large pleural effusion. Although some studies have reported that the effect of therapeutic thoracentesis is not a significant factor in late pleural thickening, we cannot exclude the possibility that this procedure affected our data.

In conclusion, pleural disease was found to continuously resolve over time and even after treatment completion. This phenomenon was related to higher levels of ESR and pleural fluid LDH but not to the amount of pleural effusion initially measured. Despite this continuous resolution after 6 months of treatment, the number of patients with significant RPO was small between 12 months and 24 months. We recommend that an intervention such as decortication should be delayed until 12 months after treatment commencement when RPO is < 60 mm after 6 months of treatment.

REFERENCES