Residual pleural thickening (RPT) is considered to be a common radiographic sequela in patients with tuberculous pleurisy (TP) after correct treatment is completed. The influence of the clinical characteristics, intensity of pleural inflammation, and type of treatment for the development of pleural thickening have been studied. The presence of a significant influence for the concentration of those pleural fluid (PF) constituents that usually are measured (i.e., proteins, lactate dehydrogenase [LDH], glucose, and pH) is controversial. Although significantly higher levels of inflammation markers such as lysozyme and tumor necrosis factor-α have been found in one series, they were found only in those patients developing pleural thickening of > 10 mm, which is a sequela rarely found nowadays. On the other hand, the presence of RPT has not been related to the chemotherapeutic regimen, the performance of a therapeutic thoracentesis, or the administration of steroids.

Because the degree of residual thickening observed in most studies was usually mild, the effect over the function has been anticipated to be of small clinical significance. However, as far as we know, the changes in pulmonary function with RPT have not been fully evaluated.

The objectives of this study were to assess the functional sequelae (FS) of patients with tuberculous pleurisy (TP), to analyze the influence of different factors in the occurrence of these FS, and, finally, to evaluate the relationship between the FS and roentgenographic sequelae.

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**Design:** An observational, retrospective study.

**Patients and methods:** From April 1986 to July 2000, all patients with a firmly established diagnosis of TP, who had been functionally studied at the end of follow-up, were included in the study. A diagnosis of TP was considered to be definitive when the presence of granuloma on a pleural biopsy specimen was demonstrated or when a culture was positive for *Mycobacterium tuberculosis* in pleural fluid (PF) or tissue. The general characteristics of the study population and PF were compared in patients with or without restrictive FS (i.e., FVC or TLC < 80%), looking for risk factors for developing this complication.

**Results:** Eighty-one of 150 patients who had been treated for TP were eligible for the study. At the end of follow-up, eight patients (10%) had a restrictive FS. These patients had a lower PF lactate dehydrogenase concentration (p < 0.001), a higher PF concentration of cholesterol (p < 0.03) and triglycerides (p < 0.03), and a higher percentage of lymphocytes (p < 0.04). A weak correlation was found between the FVC and the intensity of radiographic pleural thickening (r = −0.298; p < 0.01).

**Conclusions:** The FS in patients with TP is restrictive in type, infrequent, and usually mild. A higher PF lipid content or a more chronic inflammatory pleural reaction at diagnosis appear to be risk factors for developing a FS. The correlation between FS and roentgenographic sequelae is poor.

**Key words:** pleural effusion; pleural thickening; pulmonary function; tuberculosis

**Abbreviations:** FS = functional sequelae; IQR = interquartile range; LDH = lactate dehydrogenase; PF = pleural fluid; RPT = residual pleural thickening; RV = residual volume; TLC = total lung capacity; TP = tuberculous pleurisy

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functional sequelae (FS) occurring in patients with TP after they had undergone a correct specific therapy, to analyze the influence of different factors in the occurrence of these sequelae, and to evaluate the relationship between the intensity of the thickening and the decrease of lung volumes.

**MATERIALS AND METHODS**

**Study Population and Clinical Assessment**

All patients seen in our service with a firmly established diagnosis of TP during the period between April 1986 and July 2000, who were functionally studied at the end of follow-up, were included in the study.

The diagnosis of TP was considered to be definitive in the presence of granuloma on pleural biopsy specimen, caseating or not; or a positive culture for **Mycobacterium tuberculosis** in PF or tissue. In our hospital, until diagnosis, all patients with suspected TP are studied as inpatients.

Age, gender, smoking and alcohol intake history, and clinical symptoms were recorded. *Alcohol abuse* was defined as a daily intake of > 80 g alcohol. Weight loss was considered to be present if the patient had lost > 3 kg in the absence of a voluntary diet. In patients with productive cough, sputum smears and cultures for **M tuberculosis** were performed and recorded.

**Radiology and Interventions**

Chest radiographs were evaluated by a member of our service. The volume of the effusion was graded as *small* when the fluid contour was seen just above the costophrenic angle, *medium* when the effusion occupied at least half of the hemithorax, and *large* when the level of fluid was between the two. Diagnostic thoracentesis was performed on the first day of hospitalization, with the patient in the sitting position, using a standard 21-gauge IM needle (Microlance 21 G 1 1/2 0.8X40 Nr 2 TW.PM; Becton-Dickinson; Huesca, Spain). Values for pH, protein, glucose, cholesterol, and LDH levels, differential cell counts, and acid-fast bacilli smears and cultures from PF were recorded from the first thoracentesis. Smears and cultures of PF and biopsy specimens were processed following norms previously published. Closed pleural biopsy was performed with a Cope needle, and four biopsy samples were taken. One sample was crushed and inoculated into mycobacterial culture media, while the remaining three were processed as fixed in formaldehyde and sectioned. In our hospital, until diagnosis, all patients with suspected TP. Eighty-one patients fulfilled the conditions of the study (46 men [57%] and 35 women; mean age, 28 ± 15 years; age range, 8 to 72 years). Thirty-nine patients (48%) were smokers of a median of 7 pack-years (interquartile range [IQR], 4 to 20). The antituberculosis treatment consisted of isoniazid, 300 mg/d, rifampin 600 mg/d, and ethambutol, 20 mg/kg/d for the initial 2 months, and isoniazid and rifampin for the subsequent 7 months. Ten patients received isoniazid, rifampin, and pyrazinamide for the initial 2 months followed by an additional 4 months of therapy with isoniazid and rifampin. Steroids were added to the treatment in 26 patients at the discretion of the attending physician. The dosage used was 0.5 mg/kg/d prednisone for 1 month, with subsequent tapering of 5 mg per week.

**Radiology and Interventions**

Pleural effusions were large in 27 patients, medium in 31 patients, small in 23 patients, bilateral in 4 patients, right-sided in 44 patients, and left-sided in 33 patients. Coexistent radiographic pulmonary lesions were found in 11 of 81 patients (14%). These lesions consisted of upper lobe parenchymal infiltrates, and four of them were cavitated.

Closed pleural biopsies was performed in 77 patients. In these patients, granulomas were found in

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**Statistical Analysis**

The data are reported as the mean ± SD or the median (25th to 75th percentiles), depending on their distribution. The differences in quantitative variables between groups were assessed by means of the unpaired *t* test or the Mann-Whitney test. Correlations were evaluated by the Pearson or the Spearman regression equations, depending on the pattern of distribution. The *χ²* test was used to assess differences in categoric variables between groups. Values of *p* < 0.05 were considered to be significant.

**Results**

**Patient Demographic Data and Treatment**

During the study period, 150 patients were treated for TP. Eighty-one patients fulfilled the conditions of the study (46 men [57%] and 35 women; mean age, 28 ± 15 years; age range, 8 to 72 years). Thirty-nine patients (48%) were smokers of a median of 7 pack-years (interquartile range [IQR], 4 to 20). The antituberculosis treatment consisted of isoniazid, 300 mg/d, rifampin 600 mg/d, and ethambutol, 20 mg/kg/d for the initial 2 months, and isoniazid and rifampin for the subsequent 7 months. Ten patients received isoniazid, rifampin, and pyrazinamide for the initial 2 months followed by an additional 4 months of therapy with isoniazid and rifampin. Steroids were added to the treatment in 26 patients at the discretion of the attending physician. The dosage used was 0.5 mg/kg/d prednisone for 1 month, with subsequent tapering of 5 mg per week.

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70 patients and a biopsy specimen culture was positive for *M tuberculosis* in 43 patients. In four patients, the only diagnostic sample was a PF culture that was positive for *M tuberculosis*. A sputum culture positive for *M tuberculosis* was found in 10 patients, and a positive smear was found in 5 patients. Patients were discharged from the hospital after a mean duration of 14.8 ± 6.8 days (range, 3 to 44 days). The median number of thoracenteses performed in each patient was two (range, one to five procedures), and the total amount of PF drained between hospital admission and discharge was 1,162 ± 1,186 mL. The median duration of follow-up was 23 months (IQR, 9 to 71 months).

### Lung Function Assessment

The results of pulmonary function tests at hospital admission, at hospital discharge, and at the end of follow-up are shown in Table 1. At hospital admission, the mean FVC and TLC values were moderately reduced. Improvements in FVC and TLC at hospital discharge and at the end of the follow-up period were noted.

At the end of the follow-up period, eight patients (10%) had FVC and/or TLC < 80% of predicted with an FEV1/FVC ratio of > 80% of predicted (ie, a restrictive ventilatory defect) [Table 2]. Three patients, however, showed increased RV/TLC ratio. Two additional patients (3%), who were 69 and 33 years old, had an FEV1/FVC ratio of < 80% of predicted. These two patients were smokers of 30 and 40 pack-years of cigarettes and had received diagnoses of COPD before the pleural effusion was detected. The mean age of patients with restrictive FS was 39 ± 22 years, while that of patients without sequelae was 27 ± 14 years (p = 0.08). The general characteristics and PF biochemical parameters of patients who were grouped according to the presence or absence of restrictive FS are shown and compared in Tables 3 and 4. Patients with FS had a lower LDH concentration in PF (p < 0.001) and higher concentrations of cholesterol (p < 0.03) and triglycerides (p < 0.03), and a higher percentage of lymphocytes (p < 0.04) in PF. There were not significant differences between groups in any of the qualitative variables analyzed, however, patients with FS more frequently had a sputum smear that was positive for *M tuberculosis* (p = 0.07).

### Relationship Between FS and Radiographic Sequelae

A weak correlation was found between the FVC and the degree of radiographic pleural thickening at the end of follow-up (r = -0.298; p < 0.01). However, patients with pleural thickening had a mean FVC of 93%, which is similar to findings in those without pleural thickening (FVC, 96.4%; p = 0.45). Moreover, the sensitivity of an RPT of > 2 mm for a restrictive FS is only 50%, with a specificity of 64%. Selecting 10 mm as the cutoff point, the sensitivity would be 25% with a specificity of 96% (Table 5).

### Discussion

This study demonstrates that 10% of patients with TP who were correctly treated presented evidence of pulmonary functional impairment. However, the intensity of the functional defect is mild to moderate in most of these patients, and, although always restrictive in type, in two patients, who were both heavy smokers, an increase in RV was evident. A decrease of forced flow rates was evident in two additional patients, but a diagnosis of COPD prior to the presentation of the pleural effusion rules out any relationship between the obstructive defect and TP.

The incidence of FS is lower than that of RPT. In the present study, the incidence of RPT was 37%, but in most studies the incidence surpasses 40% when a cutoff of 2 mm is used.14,10 This seems to indicate that a patient with mild RPT does not always have an apparent functional effect. Moreover, as the present study demonstrates, the relationship between RPT and the functional restriction is weak. In fact, the sensitivity of RPT for a FS is only 50%, with a specificity of 64%. On the other hand, a functional defect may be present in the absence of RPT. So, although radiographically abnormal, an increase in pleural thickness of 2 mm seems functionally irrelevant. This casts some doubts about the appropriateness of plain radiography for the evaluation of this type of sequela. Nevertheless, in a previous study2 evaluating RPT, the sensitivity of high-resolution CT scanning (38 of 67 patients; 57%) was not significantly higher than that of radiography (35 of 70 patients; 50%).

An RPT of 10 mm was associated with an almost-significant higher probability of a decrease of lung volumes; however, the proportion of patients with this degree of pleural thickness found in our study was 6%, which is much lower than that found in other series (20%).1 It is difficult to elucidate the reasons why in the present study patients showed a

| Table 1—Changes in Pulmonary Function With Treatment*
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>Variables</strong></td>
<td><strong>Hospital Admission</strong></td>
<td><strong>Hospital Discharge</strong></td>
<td><strong>End of Follow-up</strong></td>
</tr>
<tr>
<td>FVC, %</td>
<td>60 ± 21 (21)</td>
<td>72 ± 16 (61)</td>
<td>97.6 ± 17 (81)</td>
</tr>
<tr>
<td>FEV1/FVC, %</td>
<td>103 ± 12 (21)</td>
<td>103 ± 11 (61)</td>
<td>105 ± 9 (81)</td>
</tr>
<tr>
<td>TLC, %</td>
<td>71.4 ± 16 (12)</td>
<td>70.6 ± 14 (24)</td>
<td>95.4 ± 15 (81)</td>
</tr>
</tbody>
</table>

*Values given as mean ± SD (No. of patients).
lesser degree of RPT in relation to other studies. The influence of therapeutic thoracentesis in the development of RPT has not been confirmed in every series.2,3,11 The beneficial influence of the uniform performance of sequential therapeutic thoracenteses in all patients included in this study could not be ruled out. Also, the duration of the follow-up could justify the differences between studies. There is a paucity of information regarding the time course of the development of RPT has not been confirmed in every study,2,3,11 The beneficial influence of the uniform performance of sequential therapeutic thoracenteses in all patients included in this study could not be ruled out. Also, the duration of the follow-up could justify the differences between studies. There is a paucity of information regarding the time course of the resolution for tuberculous pleural effusions.12 Al- so, the duration of the follow-up could explain the lower incidence of radiographic sequelae found in the present study in which the median follow-up duration was 23 months, which is longer than that in most other studies. In the present study, the duration of the follow-up was shorter in patients with sequelae than in those without sequelae but was without statistical significance. On the other hand, the uniform performance of thoracentesis and a long follow-up period also may have a beneficial influence on the presence of FS, justifying the relatively low frequency and intensity of restrictive sequelae that were found in the present study. The possibility that coexistent pulmonary lesions could account for the restrictive defect was not apparent from the results of the roentgenographic study. However, this study was limited to plain radiography. The observations of Stead and associates13 that most patients with TP have concomitant parenchymal disease that is radiologically subclinical, raise the possibility that CT could explain the lower incidence of radiographic sequelae found in the present study in which the median follow-up duration was 23 months, which is longer than that in most other studies. In the present study, the duration of the follow-up was shorter in patients with sequelae than in those without sequelae but was without statistical significance.

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OR
inapparent lung lesion. On the other hand, the influence (0.07), could be explained via a radiographically greater restriction, showing a trend toward significance of such parenchymal disease. In fact, the relationship studies might be useful for demonstrating the presence of such parenchymal disease. In fact, the relationship herein found between a positive sputum test result and a greater restriction, showing a trend toward significance (0.07), could be explained via a radiographically inapparent lung lesion. On the other hand, the influence (0.07), could be explained via a radiographically greater restriction, showing a trend toward significance (0.07), could be explained via a radiographically inapparent lung lesion.14 On the other hand, the influence of smoking in patients with FS seems evident in the two patients with a smoking history of > 10 pack-years who, although presenting with a restrictive defect according to the criteria used, had evidence of air trapping.

With respect to the PF constituents, only the lipid components showed an apparent influence on the development of FS. High levels of cholesterol are typical of pleural effusions having a prolonged or protracted course; however, in the present study, a correlation between the lag to the diagnosis and the presence of FS was not found.

The level of LDH in PF has been considered to be a reliable indicator of the intensity of pleural inflammation. The higher the LDH, the more inflamed the pleural surfaces are. Although RPT has been considered to be a consequence of an acute inflammatory mechanism, we found that neither the percentage of neutrophils nor protein levels influenced the later development of FS. Moreover, we have found that patients with sequelae have a significantly higher percentage of lymphocytes and lower levels of PF LDH.

Serial studies that were performed in the acute phase of the pleural effusion, after patients had undergone therapeutic thoracenteses and after the reabsorption of fluid, showed, as was expected, the restrictive effect of the accumulated PF and chest pain. The systematic practice of therapeutic thoracentesis allowed us to quantify the change of lung volumes through the treatment, irrespective of the initial pleural effusion volume.

In summary, FS in patients with TP are restrictive in type, infrequent, and usually mild. With respect to prognosis, PF characteristics that are compatible with a chronic or protracted course appear to be risk factors. The correlation between FS and roentgenographic sequelae is poor.

**References**


**Table 5—Relationship Between FS and Radiographic RPT at the End of Follow-up**

<table>
<thead>
<tr>
<th>RPT</th>
<th>Patients With FS (n = 8)</th>
<th>Patients Without FS (n = 73)</th>
<th>p Value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 2 mm (n = 30)</td>
<td>4 (50)†</td>
<td>26 (36)</td>
<td>0.460</td>
<td>1.80</td>
<td>0.417–7.834</td>
</tr>
<tr>
<td>≤ 2 mm (n = 51)</td>
<td>4 (50)</td>
<td>47 (64)‡</td>
<td>0.189</td>
<td>2.77</td>
<td>0.587–13.07</td>
</tr>
<tr>
<td>&gt; 4 mm (n = 16)</td>
<td>3 (38)†</td>
<td>13 (18)</td>
<td>0.074</td>
<td>7.78</td>
<td>1.08–55.99</td>
</tr>
<tr>
<td>≤ 4 mm (n = 65)</td>
<td>5 (63)</td>
<td>60 (82)‡</td>
<td>0.074</td>
<td>7.78</td>
<td>1.08–55.99</td>
</tr>
<tr>
<td>&gt; 10 mm (n = 5)</td>
<td>2 (25)†</td>
<td>3 (4)‡</td>
<td>0.189</td>
<td>2.77</td>
<td>0.587–13.07</td>
</tr>
<tr>
<td>≤ 10 mm (n = 76)</td>
<td>6 (75)</td>
<td>70 (96)‡</td>
<td>0.189</td>
<td>2.77</td>
<td>0.587–13.07</td>
</tr>
</tbody>
</table>

*OR = odds ratio; CI = confidence interval.
†Sensitivity of cutoff.
‡Specificity of cutoff.