Subpleural Mononuclear Cell Infiltration*

Significance in the Differential Diagnosis of Pleuritis Showing Nonspecific Histologic Findings

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To determine if patients who had lymphocyte-rich pleural effusion and a pleural biopsy without any specific findings could be histopathologically differentiated between those with tuberculous and nontuberculous pleuritis, we histologically re-evaluated the pleural biopsies of all patients whose pleural effusion was predominant with lymphocytes and contained no malignant cells. A total of 40 patients with a nonspecific histologic findings of pleural biopsy specimen were categorized based on their ultimate diagnosis as having tuberculous (n = 15), carcinomatous (n = 10) or nontuberculous, benign pleuritis (n = 15). The pleural biopsy specimen of patients with nontuberculous, benign pleuritis frequently showed a band-like infiltration of mononuclear cells in the subpleural adipose tissue with minimal pleural inflammatory infiltrate (10 out of 15 patients), while the same finding was infrequent in those with tuberculous pleuritis (0 out of 15, p = 0.0001) and pleuritis associated with carcinoma (three out of 10, p = 0.082). Based on these results, the presence of band-like infiltration of mononuclear cells in the subpleural adipose tissue with minimal pleural inflammatory infiltrate in pleural biopsy specimens of patients with lymphocyte-rich pleural effusion suggests that the pleuritis is nontuberculous in its nature.

(Chest 1990; 98:1116-20)

ADA = adenosine deaminase activity

Lymphocyte-rich pleural effusion is found in some disorders including tuberculous pleuritis.1-3 In Japan, tuberculous pleuritis is still rather common, and the differential diagnosis between tuberculous and nontuberculous pleuritis is an important clinical problem in patients with lymphocyte-rich, benign pleural effusion. The role of needle biopsy of pleura in the evaluation of unexplained pleural effusion is well established,4-6 but the significance of a biopsy, which reveals only nonspecific findings, is still unclear. Tuberculous pleuritis may eventually be diagnosed in those individuals who had a pleural biopsy specimen showing only nonspecific findings.2,9 Antituberculosis therapy may be tried in those who have lymphocyte-rich pleural effusion and a needle biopsy of the pleura without any specific finding (diagnosis ex juvantibus).10 However, the identification of which patients should undergo a trial of therapy is a difficult, yet important, clinical problem. Recently, the determination of pleural adenosine deaminase and lysozyme has been reported to be valuable in determining the differential diagnosis between tuberculous and nontuberculous pleural effusion.11 We reevaluated the histologic findings of a needle pleural biopsy of patients who had lymphocyte-rich pleural effusion and were eventually diagnosed as having either tuberculous or nontuberculous pleuritis, to examine whether there were any histologic differences other than granulomas between the pleural biopsy specimens of those who were finally diagnosed as having tuberculous and nontuberculous pleuritis.

MATERIALS AND METHODS

All patients who had pleural effusion rich in lymphocytes (lymphocytes constituted more than one half of cells in the pleural fluid) without atypical cells at the initial evaluation and were admitted during the period from January 1984 to March 1989 at Kyushu University Hospital and National Omuta Hospital were included in the study. Their cytologic specimens of pleural effusion, needle biopsy specimens of the pleura, chest roentgenograms, and medical records were reviewed. Three patients were excluded from the study because the pleural biopsy specimens consisted of only striated muscular tissue. A total of 55 patients were included in the study (Fig 1). Twelve patients showed granulomas either with (n = 6) or without necrosis (n = 6) in the pleural biopsy specimens, and the pleural effusion subsided with antituberculosis therapy. The pleural biopsy specimens of three patients revealed malignant tissue. Patients showing only nonspecific findings in the pleural biopsy specimens were categorized as having tuberculous, carcinomatous, or nontuberculous benign pleuritis based on a later definitive diagnosis. Patients were considered to have tuberculous pleuritis when the culture of pleural effusion or pleural biopsy material grew Mycobacterium tuberculosis (n = 15). Those were considered to have carcinomatous pleural disease when cancer cells were detected in the pleural effusion during the follow-up period (n = 10). The third group consisted of all those who had no evidence of tuberculous or malignant disease by an additional open biopsy procedure, or a subsequent clinical course that was inconsistent with either disease during a follow-up period of 24 to 60 months (average 38.2 months) (n = 15). Table 1 outlines the clinical and pathologic outcomes of these 15 patients. The etiology of the pleural effusion in these patients was clinically considered to be asbestosis (n = 3), congestive

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heart failure ($n=3$), collagen-vascular disease ($n=2$), postpneumonic effusion ($n=2$), postsurgical (abdominal) effusion ($n=1$), and idiopathic ($n=4$). The cultures of pleural effusion or pleural biopsy material from the second and third group patients grew no $M$ tuberculosis. The histologic findings of the needle pleural biopsies showing only nonspecific findings were reevaluated to examine whether there were any differences of the histologic findings between those of tuberculous and nontuberculous pleuritis except for granulomas. The data concerning the histologic findings were analyzed with Fisher's test. The adenosine deaminase activity was expressed as mean ± SD and analyzed with unpaired Student's $t$-test.

RESULTS

Tuberculous Pleuritis

Of 27 patients with tuberculous pleuritis, 12 patients (44.4 percent) revealed epithelioid granulomas either with (six cases) or without necrosis (six cases) in the needle biopsy specimen of the pleura. Pleural biopsy specimens of 11 patients out of these 12 showed inflammatory infiltrate composed of lymphocytes, plasma cells, and a few neutrophils. These inflammatory cells diffusely infiltrated into the pleural and subpleural tissue.

Pleural biopsy specimens of the remaining 15 cases showed only nonspecific findings. It was possible to classify the pleural histologic findings showing nonspecific findings into two patterns (Table 2). One was the pleura composed of fibrinous exudate and/or granulation and fibrous tissue. Pleural biopsy specimens of 12 patients showed this pattern, and inflammatory cell infiltration of the pleura was noted in those of seven patients (Fig 2). Such inflammatory infiltrates were found diffusely in the thickened pleura. The other pattern was the pleura thickened with only fibrosis (Fig 3). The pattern was noted in the pleural biopsy specimens of three patients, and inflammatory infiltrate of the pleura was associated in only one patient. None of the patients with tuberculous pleuritis showing nonspecific histologic findings in the pleural biopsies revealed any subpleural inflammatory infiltrate in a band-like fashion (Fig 2 and 3).

Of 15 patients with tuberculous pleuritis showing nonspecific histology, ADA activity of pleural fluid was measured in ten patients, and ranged from 20.4 to 200.0 IU/L (70.6 ± 52.1 IU/L).

Pleuritis Associated with Carcinoma

Of the 13 patients with pleuritis associated with carcinoma, three patients showed malignant tissue in the pleural biopsy specimens. Inflammatory cells, mainly lymphocytes, infiltrated around the tumor tissue to various degrees. No tumor tissue was found in the pleural biopsy specimens of the remaining ten
cases. In these patients, the pleura showed fibrosis either with or without fibrous exude. Band-like infiltration of mononuclear cells in the subpleural adipose tissue was noted in the pleural biopsy specimens of three patients, while mononuclear cells infiltrated diffusely in the pleural and subpleural tissue in those of two patients (Table 2).

Of ten patients with malignant pleuritis showing nonspecific histology, ADA activity of pleural fluid was measured in six patients, and ranged from 9.3 to 30.0 IU/L (19.5 ± 7.3 IU/L). The mean value of ADA activity was significantly lower than that in patients with tuberculous pleuritis (p<0.01).

**Nontuberculous, Benign Pleuritis**

None of 15 patients with nontuberculous, benign pleuritis showed any specific findings in the pleural biopsy specimens. However, those of ten patients (66.7 percent) revealed a band-like infiltration of mononuclear cells in the subpleural adipose tissue, while inflammatory infiltrate was minimal in the thickened pleural tissue. The incidence of subpleural inflammatory infiltrate in a band-like fashion with minimal pleural inflammatory infiltrate in patients with nontuberculous, benign pleuritis was significantly more frequent when compared to the cases of tuberculosis (p = 0.0001), and also more frequent, though statistically insignificant, when compared to those of carcinoma (p = 0.082) As in the cases of tuberculous pleuritis, the histologic condition of the pleura can also be divided into two patterns (Table 2). One was the pleura composed of fibrous exude and/or granulation and fibrous tissue. Pleural biopsy specimens of six patients revealed this pattern, four of which were associated with focal inflammatory cell infiltration in the pleura. Two out of these four patients showed a band-like infiltration of mononuclear cells in the subpleural adipose tissue. In the remaining two patients, inflammatory cell infiltration was minimal in the pleura, while a band-like infiltration of mononuclear cells was evident in the subpleural adipose tissue (Fig 4). The other pattern was that the pleura thickened with only fibrosis. Nine patients showed this pattern in the pleural biopsy specimens. Of these, inflammatory cell infiltration was noted in the pleura of one patient. In

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**Table 2—Histologic Findings of Needle Pleural Biopsy Specimens of Patients Showing Nonspecific Findings**

<table>
<thead>
<tr>
<th></th>
<th>TB (n = 15)</th>
<th>CA (n = 10)</th>
<th>Non TB, Non CA (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleura composed of fibrous exude and/or granulation and fibrous tissue</td>
<td>12 (0)</td>
<td>6 (2)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Inflammatory infiltrate in the pleura (+)</td>
<td>7 (0)</td>
<td>1 (0)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Inflammatory infiltrate in the pleura (−)</td>
<td>5 (0)</td>
<td>5 (2)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Pleura thickened with fibrous tissue</td>
<td>3 (0)</td>
<td>4 (1)</td>
<td>9 (6)</td>
</tr>
<tr>
<td>Inflammatory infiltrate in the pleura (+)</td>
<td>1 (0)</td>
<td>1 (0)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Inflammatory infiltrate in the pleura (−)</td>
<td>2 (0)</td>
<td>3 (1)</td>
<td>5 (6)</td>
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**Figure 2.** Photomicrograph of the needle pleural biopsy specimen of a patient with tuberculous pleuritis. The pleura is thickened with granulation and fibrous tissue infiltrated by chronic inflammatory cells, while little inflammatory infiltrate is seen in the subpleural fibroadipose tissue (hematoxylin-eosin, original magnification × 110).

**Figure 3.** Photomicrograph of the needle pleural biopsy specimen of a patient with tuberculous pleuritis. The pleura is thickened with fibrosis. No inflammatory infiltrate is found in the subpleural adipose tissue (hematoxylin-eosin, original magnification × 90).
six out of the remaining eight patients, inflammatory cell infiltration was minimal in the pleura, whereas mononuclear cells infiltrated in the subpleural adipose tissue in band-like fashion (Fig 5). The incidence of subpleural, band-like infiltration of mononuclear cells in each underlying disease comprising nontuberculous, benign pleuritis was as follows: asbestosis, none out of three; congestive heart failure, three out of three; collagen-vascular disease, two out of two; post-pneumonic effusion, two out of two; postsurgical (abdominal) effusion, one out of one; and idiopathic, two out of four, respectively.

Of 15 patients with nontuberculous, benign pleuritis, ADA activity of pleural fluid was measured in eight patients and ranged from 5.6 to 36.9 IU/L, (20.7 ± 10.3 IU/L). The mean value of ADA activity was significantly lower than that in patients with tuberculous pleuritis (p<0.01).

**Discussion**

A closed needle biopsy of the pleura is valuable for diagnosing tuberculous pleuritis when epithelioid granuloma exists in the biopsy specimen. However, epithelioid granulomas are considered to be scattered throughout the parietal pleura and the pleural tissue between granulomas shows a nonspecific histologic condition. As a result, some of the closed needle biopsy specimens of tuberculous pleuritis reveal only nonspecific findings. In such cases, the results of the pleural biopsy show a false negative. In fact, some patients with nonspecific biopsy specimens are confirmed subsequently as having tuberculosis. There have been many reports on the significance of negative (nonspecific) results of closed pleural biopsies. Various negative predictive values, ranging from 28 to 77 percent, have been reported, and these values are dependent upon the constitution of the patient population examined. In the present study, tuberculosis was one of the frequent causes of the pleuritis associated with lymphocyte-predominant pleural effusion and nonspecific histologic condition of the pleural biopsy. Therefore, when the initial evaluation fails to clarify the cause of the pleural effusion rich in lymphocytes (a needle biopsy of the pleura shows only nonspecific findings), we always face the problem of whether the pleuritis is tuberculous or not.

There have been few studies on the pathologic analysis of nonspecific histologic findings in pleural biopsy specimens of patients with tuberculous and nontuberculous pleuritis. The present study clarifies that the band-like infiltration of mononuclear cells in the subpleural adipose tissue with minimal pleural inflammatory infiltrate is frequently found in the pleural biopsy specimens of patients with nontuberculous, benign pleuritis, while it is rarely seen in those of tuberculous patients. Jones et al. reported the histologic condition of chronic nonspecific pleuritis, in which lymphocytic infiltrate was described. However, they did not specify the characteristics of such lymphocytic infiltrate. They also illustrated the photomicrograph of chronic nonspecific pleuritis, which seems to show mononuclear cell infiltration in subpleural adipose tissue with minimal pleural inflammatory infiltrate. There is a possibility that the difference of pleural histology between tuberculous and nontuberculous, benign pleuritis described above reflects the difference of the inflammatory stage between the two. However, such a possibility is unlikely, because in both groups, the pleural biopsies were performed within two weeks after pleural effusion was detected. Inflammatory infiltrate was also sometimes found in the subpleural tissue of the tuberculous pleuritis.

**Figure 4.** Photomicrograph of the needle pleural biopsy specimen of a patient with nontuberculous, benign pleuritis. The pleura is thickened with fibrosis. Band-like infiltration of mononuclear cells is evident in the subpleural adipose tissue (hematoxylin-eosin, original magnification ×43).

**Figure 5.** Photomicrograph of the needle pleural biopsy specimen of a patient with nontuberculous, benign pleuritis. The pleura is slightly thickened with fibrosis. Band-like infiltration of mononuclear cells is evident in the subpleural adipose tissue (hematoxylin-eosin, original magnification ×160).
such cases, however, the subpleural inflammatory infiltrate was more diffuse and contiguous to the diffuse inflammatory infiltrate in the pleural tissue. So, it was easy to differentiate such subpleural inflammatory infiltrates of tuberculous pleuritis from band-like infiltration of mononuclear cells in the subpleural adipose tissue frequently seen in cases of nontuberculous, benign pleuritis. It is unclear why the histologic findings described above were frequently found in patients with nontuberculous, benign pleuritis. Keeping in mind that both cases of collagen-vascular disease showed band-like infiltration of mononuclear cells in the subpleural adipose tissue, some systemic factors may contribute to the formation of the above histologic condition in some cases of nontuberculous, benign pleuritis. Recent reports have shown the importance of determining the pleural ADA in order to distinguish between tuberculous and nontuberculous pleural effusions. \(^\text{11}\) In the present study, ADA activity of the pleural fluid was measured in some patients. Though the mean value of the ADA activity in patients with tuberculous pleuritis was significantly higher than that in those with malignant or nontuberculous, benign pleuritis, some overlap of the ADA activity (below 40 IU/L) was present between tuberculous and nontuberculous pleural effusion. From our experience, the histologic features of the pleural biopsies mentioned above may be another means to resolve the differential diagnosis between tuberculous and nontuberculous, benign pleuritis.

The etiology of pleural effusion was undetermined in four patients in our study. A patient was considered to have neither tuberculosis nor malignancy by an open biopsy. Pleural effusion of another patient resolved spontaneously. We considered primary tuberculosis to be unlikely, as he had negative PPD and was followed for three years without any evidence of reactivation tuberculosis. The pleural effusion of the remaining two patients was unchanged after 24 and 40 months, respectively. The possibility that these two patients had tuberculous pleural disease cannot be denied completely. Even if such is the case, the incidence of subpleural mononuclear cell infiltration in a band-like fashion is still more frequent in pleural biopsies of nontuberculous, benign pleuritis (9 out of 13) when compared with that in those of tuberculous pleuritis (1 out of 17).

We must pay attention to the fact that some cases of pleuritis associated with carcinoma also showed band-like infiltration of mononuclear cells in the subpleural adipose tissue. For diagnosing malignant pleural effusion, cytologic analysis is reported to be superior to needle biopsy. \(^\text{17, 18}\) In the present study, most of the patients with malignant effusion were diagnosed as such cytologically, at an initial evaluation, and therefore, were not included in the study. However, when the histologic condition of the pleural biopsy is nonspecific and shows band-like infiltration of mononuclear cells in the subpleural adipose tissue, one cannot rule out the possibility of malignancy.

In summary, when we treat patients with lymphocyte-predominant pleural effusion whose needle biopsy specimens of the pleura show nonspecific findings, the presence of the band-like infiltration of mononuclear cells in the subpleural adipose tissue with minimal pleural inflammatory infiltrate in the pleural biopsy specimens suggests that the pleuritis is nontuberculous in its nature.

**REFERENCES**

2. Leslie WK, Kinawezitz GT. Clinical characteristics of the patient with nonspecific pleuritis. Chest 1989; 94:603-08