Chemical and immunological features of pleural effusions: comparison between rheumatoid arthritis and other diseases

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ABSTRACT The value of determination of pleural fluid glucose, pH, lactic dehydrogenase, IgG, IgA, IgM, C3, C4, anti-IgG antibody, and hydroxyproline in distinguishing between pleural effusions caused by rheumatoid arthritis (RA) and those resulting from other diseases was studied. The series comprised seven patients with RA and 115 patients with other diseases including systemic lupus erythematosus, tuberculosis, malignant disease, empyema, pneumonia, congestive heart failure, and nonspecific pleural effusion. The low glucose concentration, the low pH and the low C4 level in rheumatoid pleural effusion were the most valuable diagnostic findings. The presence of anti-IgG antibody in pleural fluid was not specific for RA. The concentration of hydroxyproline in pleural fluid and the pleural fluid-to-plasma hydroxyproline ratio were significantly higher in RA than in tuberculosis and malignant disease. The results support the view that local metabolic and immunological phenomena as well as a high turnover of collagen occur in the pleural cavity in RA.

Although pleuritis is the most common intrathoracic manifestation of rheumatoid arthritis (RA), pleural effusions occur in only 2–3% of patients.1,2 The rheumatoid pleural effusion usually occurs during the course of a previously diagnosed RA. It may, however, be the first manifestation of the disease,2 or occur secondarily to a complicating process, such as infection or neoplasia. It always presents a diagnostic problem.

Immunoglobulins are thought to diffuse from blood to pleural fluid in the same way as the other serum proteins,3,4 but the possibility of local synthesis in the pleural fluid or in the pleural membrane has not been ruled out. Anti-IgG antibody (rheumatoid factor) in pleural fluid is usually seen in patients with seropositive RA,5 and also in some patients with pneumonia, tuberculosis, or malignant disease.6 The reduced complement levels7,8 and presence of soluble immune complexes9,10 in pleural fluid from patients with RA and systemic lupus erythematosus (SLE) suggest that local immunological mechanisms are involved in the pathogenesis of pleuritis in these diseases.

The pleural fluid in RA has been described as an exudate with low glucose concentration, low pH, and high lactic dehydrogenase activity.11-14 In a preliminary communication,15 we reported that the concentration of hydroxyproline, a metabolic marker of collagen turnover,16-18 is higher in pleural effusions resulting from RA than in those resulting from tuberculosis and malignant disease. In the present study glucose, pH, lactic dehydrogenase, immunoglobulins IgG, IgA and IgM, complement components C3 and C4, anti-IgG antibody, and hydroxyproline were determined in blood and pleural fluid from patients with pleural effusions resulting from various disorders. The purpose of the study was to examine local metabolic and immunological phenomena occurring in pleuritis and to determine the value of the above-mentioned parameters in distinguishing between the pleural effusions resulting from RA and those resulting from other diseases.

Methods

The series included 122 patients out of a total of 140 consecutive patients admitted to the hospital for diagnostic evaluation of a unilateral or bilateral pleural effusion.19 These patients were examined between 1 January 1976 and 31 December 1979.
Eighteen patients were excluded because their pleural fluid was incompletely investigated. Pleural fluid was obtained by intercostal needle puncture, after which a pleural biopsy as described by Abrams was taken on suspicion of granulomatous or malignant disease. Samples of all pleural fluids were analysed cytologically, stained, and cultured for the presence of bacteria, including *Mycobacterium tuberculosis*. The diagnosis was based on clinical, radiological, and laboratory findings (including those obtained during a follow-up period of not less than one year).

Paired samples of serum and pleural fluid were obtained from all patients. Total protein was determined by the biuret reaction. Glucose concentration, pH, and lactic dehydrogenase activity were measured immediately after thoracentesis. Glucose was determined by a standard technique (Glox, Kabi Diagnostica, Sweden). Samples for determination of pH were collected anaerobically in heparinised glass capillary tubes. The pH was then measured with an ABL 2 radiometer (Copenhagen, Denmark). Lactic dehydrogenase activity was assessed by a kinetic method (Kabi, Sweden). Samples were then stored at +4°C for a maximum of seven days. Immunoglobulins IgG, IgA, and IgM and complement components C3 and C4 were determined by radial immunodiffusion (Tri-Partigen and M-Partigen plates, Behringwerke, West Germany). Anti-IgG antibody was determined by the Rose-Waaler fixation test. DNA antibody level was determined with a modified Farr RIA technique. Total hydroxyproline was determined in pleural fluid and plasma from 111 patients according to the method of Kivirikko et al.

The patients were divided into the following groups on the basis of the final diagnosis.

Seven patients (all men: mean age, 54 years; range, 44 to 70 years) had RA as diagnosed according to the criteria of the American Rheumatism Association (ARA). In four patients the diagnosis had been made before the development of pleural effusion. In one patient the pleuritis and arthritis occurred simultaneously. In two patients the pleural effusion was the first manifestation of the disease. These patients developed classical RA after one month and two years respectively. All these seven effusions were sterile on culture. Pleural biopsy was performed on two patients and showed nonspecific inflammatory changes in both. Two effusions disappeared without specific treatment and the other five disappeared after corticosteroid therapy.

Four patients (mean age, 46 years; range 18 to 67 years) had active SLE according to the criteria of the ARA. Three of these patients had joint symptoms (arthralgia or synovitis) but none had clinical signs of nephritis (proteinuria, haematuria, or renal insufficiency) at the time of the pleural effusion. Antinuclear antibodies and elevated anti-DNA antibody levels as well as hypocomplementaemia were present in the sera of three patients. In the fourth patient pleural effusion and a low C4 level in serum were the first manifestations of the disease; this patient later developed a nephrotic syndrome and a renal biopsy showed a membranous glomerulonephritis.

Twenty-eight patients (mean age, 46 years; range, 15 to 92 years) had tuberculous pleuritis. In 21 of these the diagnosis was verified by a positive culture of *Mycobacterium tuberculosis* or by a pleural biopsy showing typical epithelioid granulomas. In the remaining seven the diagnosis was based on clinical findings and a favourable response to specific antituberculous therapy.

Twenty-two patients (mean age, 63 years; range, 24 to 80 years) had pleural effusion resulting from a malignant disease. The diagnosis was based on cytology, pleural biopsy, or lung biopsy.

Six patients (mean age, 59 years; range, 40 to 80 years) had bacterial empyema.

Eleven patients (mean age, 42 years; range, 22 to 63 years) had a parapneumonic effusion.

Eleven patients (mean age, 75 years; range, 52 to 90 years) had a transudative pleural effusion. In all patients the underlying cause was congestive heart failure.

Thirty-three patients (mean age, 55 years; range, 35 to 80 years) had a nonspecific pleural effusion. During the follow-up period none of these patients developed RA.

No patient had received antituberculous, corticosteroid, or cytotoxic drugs before thoracentesis. Statistical analyses were performed using Student’s *t* test.

**Results**

Clinical and laboratory data of the patients with rheumatoid pleural effusion are shown in tables 1 and 2. On the basis of their protein concentration and lactic dehydrogenase activity all seven effusions were classifiable as exudates. Pleural fluid glucose was low in six patients, four of whom had had symptoms related to pleuritis for two months or longer, and was normal in one patient whose pleuritic symptoms had persisted for three weeks before thoracentesis. All five effusions investigated demonstrated acidosis (pH < 7.30). The total leucocyte count of the effusions varied greatly. Lymphocytic predominance (>50% of all leucocytes) was seen in five, neutrophilic in one, and eosinophilic in one. In two patients, the concentration of IgG was higher in
pleural fluid than in serum and one of these patients also had a higher IgM level in pleural fluid than in serum. C3 levels were markedly decreased in three and C4 levels were very low in all seven effusions. Anti-IgG antibody was present in serum from all patients and in six of the effusions. The concentration of hydroxyproline in all patients was greater in pleural fluid than in plasma.

The low glucose concentration distinguished the rheumatoid effusions from all other effusions except the empyemas (table 3). Three patients had diabetes mellitus and their glucose concentrations are not included in the table. The pH in the rheumatoid effusions was significantly lower than in the tuberculous, malignant, transudative, and nonspecific effusions and significantly higher than in the empyemas. The pH of the rheumatoid effusions was also lower than the pH of the effusions caused by SLE but the difference was not statistically significant. Rheumatoid effusions had significantly higher lactic dehydrogenase activity than tuberculous, malignant, transudative, and nonspecific effusions.

To render pleural effusions of different aetiology comparable the concentrations of IgG, IgA, IgM, C3, and C4 were related to the concentration of total protein and expressed as g per 100 g protein. Pleural fluid from patients with RA contained significantly higher concentrations of IgG than pleural fluid from patients with tuberculosis and significantly higher concentrations of IgM than pleural fluid from patients with malignant disease and congestive heart failure (table 4). C3 and C4 were measured in 118 pleural fluids. The concentration of C3 was significantly lower in pleural fluid from patients with RA than in pleural fluid from patients with tuberculosis, malignant disease, pneumonia, congestive heart failure, and nonspecific pleural effusion (fig 1). Determination of the C4 level in pleural fluid segregated patients with RA from patients with SLE and empyema also (fig 2).

Ten patients with nonrheumatoid disease had measurable titres of anti-IgG antibody in their pleural fluid (table 5). No anti-IgG antibody was found in the sera of three of these patients (one with tuberculosis, one with metastatic thyroid carcinoma,
Pleural effusion in rheumatoid arthritis

Table 3 Concentrations of protein and glucose, pH, and lactic dehydrogenase activity in pleural fluid of 122 patients with pleural effusion of varying aetiology

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>Number</th>
<th>Protein (g/l)</th>
<th>Glucose (mmol/l)</th>
<th>pH</th>
<th>LDH (U/l)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>7</td>
<td>53 ± 15</td>
<td>1-0 ± 1-6</td>
<td>7-13 ± 0-06</td>
<td>2343 ± 2123</td>
<td></td>
</tr>
<tr>
<td>Systemic lupus erythematous</td>
<td>4</td>
<td>50 ± 8-7</td>
<td>4-5 ± 0-6</td>
<td>&lt;0-005</td>
<td>7-29 ± 0-03</td>
<td>NS</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>28</td>
<td>49 ± 7</td>
<td>3-8 ± 1-3</td>
<td>&lt;0-001</td>
<td>7-31 ± 0-07</td>
<td>&lt;0-001</td>
</tr>
<tr>
<td>Malignant disease</td>
<td>22</td>
<td>45 ± 8</td>
<td>5-0 ± 2-1</td>
<td>&lt;0-001</td>
<td>7-37 ± 0-08</td>
<td>&lt;0-001</td>
</tr>
<tr>
<td>Empyema</td>
<td>6</td>
<td>69 ± 18</td>
<td>0-2 ± 0-2</td>
<td>&lt;0-01</td>
<td>6-89 ± 0-15</td>
<td>&lt;0-01</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>11</td>
<td>47 ± 6</td>
<td>4-4 ± 1-8</td>
<td>&lt;0-005</td>
<td>7-28 ± 0-18</td>
<td>NS</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>11</td>
<td>25 ± 10</td>
<td>&lt;0-001</td>
<td>7-40 ± 0-10</td>
<td>&lt;0-001</td>
<td></td>
</tr>
<tr>
<td>Nonspecific pleural effusion</td>
<td>33</td>
<td>47 ± 6</td>
<td>4-9 ± 1-6</td>
<td>&lt;0-001</td>
<td>7-33 ± 0-14</td>
<td>&lt;0-001</td>
</tr>
</tbody>
</table>

*p = probability value compared with rheumatoid arthritis (Student’s t test)
†Not done in two patients with rheumatoid arthritis and in one with systemic lupus erythematous
§LDH = lactic dehydrogenase
/ Mean ± SD
NS = not significant

Conversion: SI to traditional units—Glucose: 1 mmol/l = 18 mg/100 ml.

Table 4 Concentrations of IgG, IgA, and IgM corrected for total protein in pleural fluid of 122 patients with pleural effusion of varying aetiology

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>Number</th>
<th>IgG (g/100 g protein)</th>
<th>IgA (g/100 g protein)</th>
<th>IgM (g/100 g protein)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>7</td>
<td>27-6 ± 10-4†</td>
<td>5-7 ± 3-1</td>
<td>2-9 ± 1-2</td>
<td></td>
</tr>
<tr>
<td>Systemic lupus erythematous</td>
<td>4</td>
<td>30-0 ± 10-7</td>
<td>4-3 ± 0-8</td>
<td>2-4 ± 1-4</td>
<td>NS</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>28</td>
<td>21-0 ± 4-8</td>
<td>&lt;0-02</td>
<td>6-4 ± 3-0</td>
<td>NS</td>
</tr>
<tr>
<td>Malignant disease</td>
<td>22</td>
<td>20-5 ± 5-0</td>
<td>&lt;0-05</td>
<td>4-0 ± 1-3</td>
<td>&lt;0-005</td>
</tr>
<tr>
<td>Empyema</td>
<td>6</td>
<td>19-3 ± 8-4</td>
<td>NS</td>
<td>5-5 ± 3-2</td>
<td>&lt;0-01</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>11</td>
<td>26-9 ± 6-5</td>
<td>NS</td>
<td>4-8 ± 2-1</td>
<td>&lt;0-05</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>11</td>
<td>27-7 ± 6-6</td>
<td>NS</td>
<td>6-0 ± 2-2</td>
<td>&lt;0-005</td>
</tr>
<tr>
<td>Nonspecific pleural effusion</td>
<td>33</td>
<td>21-9 ± 5-2</td>
<td>&lt;0-05</td>
<td>5-1 ± 3-3</td>
<td>NS</td>
</tr>
</tbody>
</table>

*p = probability value compared with rheumatoid arthritis (Student’s t test)
†Mean ± SD
NS = not significant

and one with congestive heart failure and klebsiella septicaemia). C3 levels were not depressed in any of these 10 fluids. The concentration of C4 was low (range 0-06 to 0-10 g/l) in four of these fluids.

The concentration of total hydroxyproline in the plasma from all patient groups corresponded to the reference values (table 6). In patients with RA, tuberculosis, and nonspecific pleural effusion the concentration of hydroxyproline was significantly greater in pleural fluid than in plasma (p < 0-001, p < 0-005, and p < 0-001, respectively). Comparison of various diseases showed that patients with RA had a significantly higher pleural fluid hydroxyproline concentration and a significantly higher pleural fluid-to-plasma hydroxyproline ratio than patients with tuberculosis or malignant disease.

Discussion

Although RA is three times more common in women than in men, the majority of patients with rheumatoid pleural effusion are men and most are middle-aged. In the present study all seven patients with pleural effusion and RA were men and six were between 44 and 55 years old. The reasons for this male preponderance remain unknown.

The clinical features of pleural effusion in RA are the same as those of pleural involvement in any other disease. Moreover, the rheumatoid pleural effusion has no pathognomonic features and pleural biopsy in rheumatoid pleuritis only seldom shows rheumatic nodules. However, a low glucose concentration, a low pH, and a high lactic dehydrogenase activity are characteristic of rheumatoid pleural fluid, except when the effusion is of recent origin. In the present study, these parameters helped to distinguish the rheumatoid effusions from all other effusions except the empyemas. The high lactic dehydrogenase activity in rheumatoid pleural effusion probably reflects a marked inflammatory response. In rheumatoid pleuritis, metabolically active pleural lining cells probably consume glucose, thus causing an impaired transport of glucose from blood to pleural fluid. The end products of glucose metabolism, lactate and carbon dioxide, then accumulate in the pleural space and are responsible for the pleural fluid acidosis. These metabolic events also occur in the rheumatoid synovia, where...
they create the optimal milieu for the acid hydrolases, which are involved in the tissue breakdown in the rheumatoid joint.

Increased pleural capillary permeability in the areas of the rheumatic nodules is probably responsible for the formation of pleural fluid in RA. The concentrations of proteins in pleural fluid are usually lower than the corresponding values in serum. In the same way as other proteins, immunoglobulins are thought to diffuse from blood to pleural fluid in inverse proportion to their molecular weight. In our study the presence of anti-IgG antibody in blood and pleural fluid in two patients in whom pleural effusion was the first and only manifestation of the rheumatic disease indicates that cells in the pleural membrane, like cells in the synovial membrane, can synthesise immunoglobulins in RA. Rheumatoid pleural fluid usually does not contain plasma cells but has a considerable lymphocyte population. As most of them are T lymphocytes, pleural fluid lymphocytes probably do not contribute significantly to the immunoglobulin content of the fluid.

Determination of immunoglobulins in pleural fluid was of limited value in the differential diagnosis of pleural effusions. The lower concentration of IgM in malignant effusions than in rheumatoid effusions is, however, worthy of note. More significantly, the low C3 level in pleural fluid distinguished RA from all other diagnoses, except SLE and empyema. Determination of the C4 concentration in pleural fluid proved even more helpful; it was significantly lower in RA than in any other disease.

The reduced complement levels in rheumatoid pleural effusions but normal levels in blood is in agreement with the presence of immune complexes in pleural fluid and points to the importance of local immunological processes in the pleura. Our data agree with earlier reports that complement activation in rheumatoid pleural effusion occurs essen-

![Graph showing C3 levels in various pleural effusions](image_url)
Pleural effusion in rheumatoid arthritis

Fig 2 Concentration of C4 corrected for total protein in pleural fluid from 118 patients with pleural effusion of varying aetiology. The horizontal lines indicate the mean values for each group. RA = rheumatoid arthritis; p = probability value by Student's t test.

Table 5 Titre of anti-IgG antibody in pleural fluid and serum from 10 patients with pleural effusion resulting from nonrheumatic disease

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Anti-IgG antibody*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pleural fluid</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>1:64</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>1:32</td>
</tr>
<tr>
<td>Pulmonary epidermoid carcinoma</td>
<td>1:250</td>
</tr>
<tr>
<td>Pulmonary epidermoid carcinoma</td>
<td>1:128</td>
</tr>
<tr>
<td>Follicular thyroid carcinoma</td>
<td>1:64</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1:128</td>
</tr>
<tr>
<td>Congestive heart failure, sepsis</td>
<td>1:500</td>
</tr>
<tr>
<td>Nonspecific pleural effusion</td>
<td>1:250</td>
</tr>
<tr>
<td>Nonspecific pleural effusion</td>
<td>1:32</td>
</tr>
<tr>
<td>Nonspecific pleural effusion</td>
<td>1:32</td>
</tr>
</tbody>
</table>

*Measured with the Rose-Waaler fixation test

Levine et al, who, using the Latex fixation test, reported rheumatoid-factor-like activity to be present in a significant titre (≥1:160) in pleural fluid.
from 15 to 45% of patients with tuberculosis, malignant disease, and bacterial pneumonia, we found the frequency of measurable anti-IgG antibody titres in pleural fluid to be much lower. Moreover, a titre of 1:1000 or higher in pleural fluid was found only in patients with RA. The presence of ragocytes, or neutrophilic granulocytes containing cytoplasmic inclusions, in pleural fluid is not specific for RA as these cells have also been observed in tuberculosis and malignant disease.35 36

The urinary excretion of hydroxyproline is an indicator of the turnover of collagen and reflects either the formation or the breakdown of mature connective tissue.16 18 Plasma hydroxyproline is increased in RA and in various other disease states.37 In patients with RA the hydroxyproline concentration in synovial fluid correlates positively with the activity of the disease38 and with the number of lymphocytes in synovial fluid.39 We observed that patients with RA, tuberculosis, and nonspecific pleural effusion had significantly higher concentrations of hydroxyproline in pleural fluid than in plasma, which suggests that a local turnover of collagen occurs in the pleural cavity in these disease states. It has been shown that lymphocytes produce a factor which stimulates collagenase production by rheumatoid synovial cells in vitro.40 The high hydroxyproline concentration and the high pleural fluid-to-plasma hydroxyproline ratio in rheumatoid pleural effusion could be initiated by local lymphocyte activity in the pleural fluid or in the pleural membrane. In the differential diagnosis of pleural effusions the determination of hydroxyproline in pleural fluid distinguished rheumatoid pleural effusion from those of tuberculous and malignant origin.

In conclusion our results show that determination of glucose, pH, and C4 in pleural fluid are the three most valuable tests in the diagnosis of pleural effusion in RA. The present study also indicates that in RA a high turnover of collagen takes place in the pleural cavity. The question of the unitary concept of rheumatoid inflammation will be better understood by further studies on the articular and extra-articular manifestations of the disease.

This work was supported by grants from the Finska Läkaresällskapet, the Jalmari and Rauha Ahokas Foundation, and the Finnish Antituberculosis Association.

### References


### Table 6  Concentration of total hydroxyproline in pleural fluid and plasma and the pleural fluid-to-plasma hydroxyproline ratio in 111 patients with pleural effusion of varying aetiology

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number</th>
<th>Hydroxyproline (μmol/l) pleural fluid</th>
<th>p*</th>
<th>Hydroxyproline (μmol/l) plasma</th>
<th>p</th>
<th>Pleural fluid-to-plasma p hydroxyproline ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>7</td>
<td>20.6 ± 3.8†</td>
<td></td>
<td>10.4 ± 3.5</td>
<td></td>
<td>2.23 ± 1.00</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>3</td>
<td>17.3 ± 3.2</td>
<td>NS</td>
<td>12.7 ± 6.8</td>
<td>NS</td>
<td>1.42 ± 0.52</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>27</td>
<td>10.8 ± 3.7</td>
<td>&lt;0-001</td>
<td>7.9 ± 3.2</td>
<td>NS</td>
<td>1.45 ± 0.50</td>
</tr>
<tr>
<td>Malignant disease</td>
<td>22</td>
<td>13.8 ± 4.5</td>
<td>&lt;0-001</td>
<td>12.1 ± 3.9</td>
<td>NS</td>
<td>1.16 ± 0.18</td>
</tr>
<tr>
<td>Empyema</td>
<td>6</td>
<td>15.0 ± 5.1</td>
<td>NS</td>
<td>10.5 ± 3.4</td>
<td>NS</td>
<td>1.46 ± 0.35</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>9</td>
<td>15.2 ± 9.2</td>
<td>NS</td>
<td>11.5 ± 6.0</td>
<td>NS</td>
<td>1.33 ± 0.34</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>9</td>
<td>17.3 ± 7.3</td>
<td>NS</td>
<td>12.8 ± 5.8</td>
<td>NS</td>
<td>1.36 ± 0.35</td>
</tr>
<tr>
<td>Nonspecific pleural effusion</td>
<td>28</td>
<td>16.2 ± 5.2</td>
<td>NS</td>
<td>11.3 ± 4.5</td>
<td>NS</td>
<td>1.55 ± 0.46</td>
</tr>
</tbody>
</table>

*p = probability value compared with rheumatoid arthritis (Student's t test)

†Mean ± SD

NS = not significant

Conversion: SI to traditional units—Hydroxyproline: 1 μmol/l = 13.1 μg/100 ml.
Pleural effusion in rheumatoid arthritis


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