Clinical and laboratory features of lupus patients with complicating pulmonary disease

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The objective of this study was to determine the incidence of pulmonary involvement in patients with systemic lupus erythematosus (SLE) and to clarify the clinical and laboratory characteristics in SLE patients with various pulmonary involvements.

A retrospective study (n=137) revealed that the types of pulmonary involvement found in SLE patients were: pleuritis (9%), interstitial pneumonia (8%), pulmonary infarction (7%), pulmonary infection (4%), pulmonary hypertension (2%), restrictive dysfunction (28%) and decreased diffusion capacity (43%). The incidences of pericarditis (P<0.01), arthralgia (P<0.05) and hypoalbuminemia (P<0.05) were significantly greater in patients with pleuritis than in those without, while in patients with interstitial pneumonia, the incidence of anti-SS-A antibody (P<0.05) and sicca syndrome (P<0.05) were significantly greater than in those without. A longitudinal follow-up study of patient groups with various pulmonary involvements revealed: 1. significant changes of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), lactate dehydrogenase (LDH) and thrombomodulin (TM) in patients with pleuritis, and 2. significant changes of WBC and LDH in patients with interstitial pneumonia.

The increased ESR, CRP and TM levels during disease episodes suggest that the involvement of inflammatory processes is related to vasculitic events in the pathogenesis of lupus pleuritis. A higher incidence of anti-SS-A antibody in lupus patients with interstitial pneumonia suggests a potential role for this autoantibody in the pathogenesis of this complication.

Introduction

Systemic lupus erythematosus (SLE) is a chronic systemic disease which can involve many organ systems such as the central nervous system, lung, kidney and skin. Patients with SLE have been shown to have a number of pulmonary complications, including pleuritis, interstitial pneumonia, pulmonary hypertension, pulmonary infarction, pulmonary haemorrhages and infectious pneumonia (1–4). Moreover, abnormalities in pulmonary function tests such as restrictive changes and a decreased diffusion capacity for carbon monoxide (DLCO) have been reported in patients with SLE regardless of the apparent pulmonary involvement (5). In the present study, we analysed the types and frequencies of pulmonary involvement and characterized the clinical and laboratory findings in lupus patients with pulmonary diseases.

Patients and Methods

PATIENTS

One hundred and thirty-seven consecutive patients with SLE who were being actively followed-up by the Collagen Disease Clinic at the International Medical Center of Japan were identified from the files. Patients with SLE who fulfilled four or more of the revised American College of Rheumatology (ACR) criteria for SLE (6) and whose clinical records were available for review were selected in June 1995. The following data were collected: sex; age; year of disease onset; complete clinical history, including arthralgia, fever, cutaneous lesions, photosensitivity, alopecia, cardiovascular disease, Raynaud's phenomenon, respiratory disease, genitourinary disease, central nervous system and psychiatric disorders, abdominal complaints, oral ulcers, serositis, sicca symptoms; and a complete list of present medications.
The mean ± SD and range of the age at observation, the age at onset and the duration of disease were 42 ± 12 years and 20–79 years; 27 ± 11 years and 5–58 years and 15 ± 7 years and 4–39 years, respectively. The female: male ratio was 127:10.

Using the patients’ notes, which charted the entire clinical history of the disease, the presence or absence of the following clinical and laboratory findings were investigated in the 137 patients: malar or discoid rash, photosensitivity, oral ulcers, alopecia, arthritis, arthralgia, pericarditis, pleuritis (defined by the presence of characteristic pain, characteristic friction rub, and radiographical findings), interstitial pneumonia (defined by radiographical and/or computerized tomographic findings), pulmonary infarction (defined by pulmonary angiography and/or lung scanning), pneumonia (defined by bacterial and fungal infection of which the causative agents were determined), pulmonary hypertension (defined by a mean pulmonary artery pressure exceeding 25 mmHg which was measured by right cardiac catheterization or Doppler echocardiography), restrictive pulmonary disease [a forced vital capacity (FVC) of <80% predicted], decreased DLCO (<70% predicted), convulsions, psychosis, thrombosis, spontaneous abortions, sicca syndrome, persistent proteinuria ≥0.5 g day⁻¹ or greater than 3+ if quantification was not performed), cellular casts, decreased creatinine clearance (Cr, ≤60 ml min⁻¹), haemolytic anaemia, leukopenia (<4000 mm⁻³), lymphopenia (<1500 mm⁻³), thrombocytopenia (<100 mm⁻³), presence of fluorescent anti-nuclear antibodies (FANA), LE cells and positive LE test, presence of anti-double stranded (ds) DNA antibodies, anti-U1-RNP, anti-Sm, anti SS-A and anti SS-B antibodies [assayed using enzyme-linked immunosorbent assay (ELISA) kits (Medical Biological Laboratory, Nagoya, Japan), anti-cardiolipin antibodies, circulating immune complexes, low C3 (<60 mg dl⁻¹) and low C4 (<10 mg dl⁻¹) levels, biological false positives for syphilis (BFPs), lupus anticoagulants, hypoalbuminemia (<3.5 g dl⁻¹) and elevated erythrocyte sedimentation rate (ESR, ≥30 mm h⁻¹).

The presence or absence of the following clinical and laboratory findings was studied longitudinally, in 23 SLE patients with pulmonary involvement (12 with pleuritis and 11 with interstitial pneumonia) 6 months before an episode (-6M), during an episode (0M) and at 6 months after an episode (+6M), from May 1979 to July 1994 by a retrospective chart review: malar rash, discoid rash, photosensitivity, alopecia, oral ulcers, arthritis, convulsions, psychosis, pleuritis, pericarditis, dyspnoea, sputum, chest pain, cough or fine crepitation, pulmonary hypertension (mean pulmonary artery pressure >25 mmHg), proteinuria ≥0.5 g day⁻¹, cellular cast, haemolytic anaemia, leukopenia (<4000 mm⁻³), lymphopenia (<1500 mm⁻³), thrombocytopenia (<100 mm⁻³). BFPs, FANA, medication (oral corticosteroid, corticosteroid pulse therapy or immunosuppressants). Values for the following were obtained in laboratory studies: IgG anti-ds and single-stranded DNA antibodies, IgG, IgM, IgA, circulating immune complexes, C3, C4, ESR, C-reactive protein (CRP), white blood cell count (WBC), lactate dehydrogenase (LDH), thrombomodulin (TM) and prednisolone levels.

Disease activity in the lupus patients was scored by counting the number of the following variables present: 1. fever (>37°C), 2. arthralgia, 3. malar rash, 4. oral ulcers or alopecia, 5. hypocomplementemia (C3: ≥60 mg dl⁻¹ or C4: ≥10 mg dl⁻¹), 6. hypoalbuminemia (<3.5 g dl⁻¹), 7. elevated ESR (≥30 mm h⁻¹), 8. LE cells or positive LE test. The disease activity score was evaluated at -6M, 0M, and at +6M. Patients were judged to be suffering from active disease when the score was ≥4.

METHODS

Assay for thrombomodulin

Thrombomodulin levels in serum samples which had been stored at −20°C were measured using a one-step sandwich ELISA developed by Fuji Chemical Industries (Takaoka, Japan) (7).

STATISTICAL ANALYSIS

Data are reported as means ± SD. Data analysis was performed with StatFlex software (ViewFlex Co. Ltd., Tokyo, Japan) using the Wilcoxon test, chi-squared test, Fisher’s exact test. Spearman’s rank-sum test or the Mann-Whitney U-test as appropriate. Differences of P<0.05 were considered statistically significant.

Results

Table 1 shows the types and frequencies of pulmonary involvement found in the 137 SLE patients. Isolated DLCO reduction without restrictive or obstructive change was found in 14 of 74 (19%) patients. No statistically significant differences in mean age or sex ratio were found between patients with pulmonary involvement or abnormal pulmonary function tests and those who did not have these pulmonary problems.

The incidence of abnormal clinical and laboratory findings throughout the clinical history of the disease in lupus patients with pulmonary involvement was compared to that in patients with no pulmonary involvement. As shown in Fig. 1(a), the incidences of pericarditis (P<0.01), arthralgia (P<0.01) and hypoalbuminemia (P<0.05) were significantly greater in patients with pleuritis than in those without, while the incidence of anti-SS-A antibody was significantly lower (P<0.05) in patients with pleuritis than in those without, while the incidence of malar rash (P<0.05) was significantly lower. Patients with pulmonary infarction had a significantly greater incidence of lupus anticoagulants (P<0.01), decreased DLCO (P<0.05), spontaneous abortion (P<0.05) and decreased Ccr (P<0.05) than those without pulmonary infarction [Fig. 1(c)]. In patients with pulmonary infections (n=5), the frequency of decreased DLCO (4, 80%) was significantly greater than those without pulmonary infections (27, 20%, P<0.01;
Fisher's exact test). Patients with restrictive dysfunction (%FVC <50% predicted) and a significantly greater incidence of elevated erythrocyte sedimentation rate (P<0.01) and LE test [P<0.05, Fig. 1(d)] and those with decreased diffusion capacity (DLCO: <70% predicted) had a significantly greater incidence of Raynaud's phenomenon (P<0.001), proteinuria (P<0.01), leukopenia (P<0.01), lymphopenia (P<0.05) and decreased Ccr [P<0.05, Fig. 1(e)].

The median and interquartile ranges of the prednisolone dosage given at OM (40 and 5-10 mg day⁻¹) were significantly higher than those recorded at -6M (10 and 0-10 mg day⁻¹, P<0.05) and those at +6M (10 and 20-40 mg day⁻¹, P<0.05). In addition, methylprednisolone pulse therapy was administered to one (3%) of 12 patients, while an immunosuppressive agent (cyclophosphamide) was given to three (25%) patients. The follow-up study of lupus patients with pleuritis revealed that: 1. the incidence of dyspnoea at OM (5, 42%) was significantly higher than at +6M (0, 0%, P<0.05); 2. the frequency of chest pain at OM (7, 58%) was significantly higher than at -6M (1, 8%, P<0.05) and at +6M (1, 9%, P<0.05); 3. the incidence of coughs at OM (5, 42%) was significantly higher than at -6M (0, 0%, P<0.05) and at +6M (0, 0%, P<0.05); 4. the incidence of pericarditis at OM (5, 42%) was significantly higher than at -6M (0, 0%, P<0.05) and at +6M (0, 0%, P<0.05); 5. the number of patients with active disease at OM (7, 58%) was significantly higher than at -6M (1, 8%, P<0.05) and at +6M (0, 0%, P<0.05); 6. the median and interquartile ranges of IgA at -6M (294, 250-250 mg dl⁻¹) were significantly higher than at 0M (261, 179-387 mg dl⁻¹) and at +6M (223, 167-436 mg dl⁻¹, P<0.05); 7. the median and interquartile ranges of the ESR (Westergren) at 0M (80, 44-112 mm h⁻¹) were significantly higher than at +6M (35, 9-44 mm h⁻¹, P<0.05); 8. the median and interquartile ranges of CRP levels at 0M (49, 21-63 mg dl⁻¹) were significantly higher than at +6M (0.5, 0.2-0.7 mg dl⁻¹, P<0.05); 9. the median and interquartile ranges of LDH at 0M (347, 215-417 mg dl⁻¹) were significantly higher than at -6M (201, 187-288 mg dl⁻¹, P<0.05) and at +6M (231, 194-309 mg dl⁻¹, P<0.01, Fig. 2(a)); and 10. the median and interquartile ranges of the TM levels at 0M (8.6, 3.2-9.9 FU ml⁻¹) were significantly higher than at -6M (3.5, 2.5-4.5 FU ml⁻¹, P<0.05) and at +6M (4.6, 2.6-6.3 FU ml⁻¹, P<0.01, Fig. 3(a)).

The median and interquartile range of the dosage of prednisolone given at OM (40, 5-60 mg day⁻¹) was significantly higher than those at -6M (12.5, 5-23.8 mg day⁻¹, P<0.05) and at +6M (7.5, 5-15 mg day⁻¹, P<0.05). In addition, methylprednisolone pulse therapy was undertaken in four (36%) of the 11 patients and immunosuppressive agents were given to three (27%) patients (cyclophosphamide to two and azathioprine to the other).

The follow-up study of lupus patients with interstitial pneumonia revealed that: 1. the incidence of dyspnoea at OM (5, 45%) was significantly higher than at +6M (0, 0%, P<0.05); 2. the incidence of coughing at OM (7, 64%) was significantly higher than at +6M (1, 9%, P<0.05); 3. the incidence of sputum at OM (7, 64%) was significantly higher than at -6M (1% 9%, P<0.05) and at +6M (1, 9%, P<0.05); 4. the incidence of fine crepitation at OM (5, 45%) was significantly higher than at +6M (0, 0%, P<0.05); 5. the median and interquartile ranges of the WBC at OM (8200, 5950-11300 mm⁻³) were significantly higher than those at -6M (6100, 4000-6850 mm⁻³, P<0.05) by Wilcoxon test; 6. the median and interquartile range of the LDH levels at 0M (271, 197-580 IU l⁻¹) were significantly higher than those at -6M [204, 161-252 IU l⁻¹, P<0.01; Fig. 2(b)].

The median and interquartile ranges of the ESR (80, 44-112 mm h⁻¹), CRP (4.85, 2.10-6.25 mg dl⁻¹) and WBC (8200, 5950-11300 mm⁻³) in patients with pleuritis were significantly higher than in patients with interstitial pneumonia (45, 37-0.60.5 mm h⁻¹, P<0.05; 0.60, 0.20-3.75 mg dl⁻¹, P<0.05; 6100, 4000-6850 mm⁻³, P<0.05).

### Table 1. Types and frequencies of pulmonary involvement or abnormal pulmonary function tests in patients with SLE

<table>
<thead>
<tr>
<th>Types of pulmonary involvement or abnormal pulmonary function tests</th>
<th>Frequencies n (%)</th>
<th>Mean ± SD</th>
<th>Sex ratio F:M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleuritis</td>
<td>12 (9)</td>
<td>45 ± 15</td>
<td>10:2</td>
</tr>
<tr>
<td>Interstitial pneumonia</td>
<td>11 (8)</td>
<td>47 ± 10</td>
<td>11:1</td>
</tr>
<tr>
<td>Pulmonary infarction</td>
<td>9 (7)</td>
<td>47 ± 8</td>
<td>9:0</td>
</tr>
<tr>
<td>Pulmonary infection</td>
<td>5 (4)</td>
<td>41 ± 15</td>
<td>2:0</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>2 (2)</td>
<td>32 ± 4</td>
<td>2:0</td>
</tr>
<tr>
<td>Restrictive changes</td>
<td>23 (29)*</td>
<td>43 ± 16</td>
<td>23:1</td>
</tr>
<tr>
<td>Decreased DLCO</td>
<td>33 (45)†</td>
<td>44 ± 12</td>
<td>30:2</td>
</tr>
<tr>
<td>Whole SLE</td>
<td>137</td>
<td>42 ± 12</td>
<td>127:10</td>
</tr>
</tbody>
</table>

DLCO = diffusion capacity for carbon monoxide; n = number of patients; *Forced vital capacity was tested in 78 patients and †DLCO in 74 patients.
Fig. 1. Conditions with significantly different frequencies between patients with and without pleuritis (a), interstitial pneumonia (b), pulmonary infarction (c), restrictive dysfunction (d) and decreased diffusion capacity (e). Significantly more frequent compared to patients without the respective pulmonary involvement (**: P < 0.01, *: P < 0.05) and significantly less frequent compared to patients without the respective pulmonary involvement (#: P < 0.05).

Discussion

We have demonstrated a significant incidence of pulmonary complications, such as pleuritis, interstitial pneumonia and pulmonary infarction, during the history of the disease in patients with SLE.

In SLE patients with pleuritis as a complication, the incidence of pericarditis, arthralgia and hypoalbuminemia...
were significantly greater than in those without pleuritis. Estes et al. (2) reported that 16 out of 60 (27%) lupus patients with pleuritis had nephrotic syndrome. In our study, four out of 12 (33%) such patients had nephrotic syndrome. Our longitudinal study of patients with pleuritis revealed significant elevation of serum TM levels during episodes, suggesting that some mechanism related to damage of the endothelial cells (i.e. increased capillary permeability) might be involved in the pathogenesis of pleuritis (8). Conditions such as arthralgia and hypalbuminemia were thought to be associated with SLE activity and in fact seven (58%) of our patients with pleuritis had active disease at the time of their pleuritic episode.

The levels of ESR and CRP and WBC counts during episodes of SLE in patients with pleuritis were greater than those in lupus patients with interstitial pneumonia. Usually, SLE patients with active disease tend not to have significantly elevated CRP levels (9,10) and often have leukopenia. Thus, the elevation of CRP and WBC counts during SLE episodes in these pleuritic patients was somewhat peculiar, suggesting the involvement of specific inflammatory processes in the pathogenesis of lupus pleuritis, probably in response to specific cytokines released by activated immunoinflammatory cells. Moreover, a large mass of inflammatory cells, which is characteristic of pleuritis, may lead to elevation of CRP and WBC. Bouros et al. (11) reported that massive bilateral pleural effusion could be the only first manifestation of SLE. Although our pleuritic patients had all developed full-blown disease at the onset of pleuritis, SLE should always be borne in mind when examining patients whose sole symptom is massive pleural effusion.

In SLE patients with the complication of interstitial pneumonia, the incidences of anti-SS-A antibodies and sicca syndrome were significantly greater than in those without pulmonary involvement. Boulware et al. (12) reported an incidence of 25% for lupus pneumonitis among 63 SLE patients and revealed that as many as 81% of patients with lupus pneumonitis have anti-SS-A (Ro) antibodies, compared with 38% for the entire group with SLE (P<0.001). Simmons-O’Brien et al. (13) followed 100 patients (including 50 with SLE) who were positive for anti-SS-A antibody and found five with SLE and interstitial pneumonia. Hedgpeth et al. (14) reviewed all inpatients seen at their rheumatology service from 1984 to 1986 and found that 10 of the 12 patients with SLE and interstitial pneumonia had antibodies to SS-A.

The association of lupus pneumonitis and anti-SS-A antibodies may result from a speculative immunopathogenic role of the antibody to SS-A antigen. It has been suggested that in SLE, immune complexes with anti-SS-A antibodies are selectively deposited within the lung, thus initiating an inflammatory response. Alternatively, any
inflammatory stimulus inciting alveolitis may induce reactive alveolar lining cells to increase the expression of the SS-A antigen on their cell surfaces, as is seen in keratinocytes after UV light irradiation (15). This SS-A surface antigen could bind to anti-SS-A antibodies in the circulation, thereby enhancing the inflammatory reaction. Moreover, it is possible that cross-reactivity between the SS-A antigen and other similar alveolar cell surface epitopes occurs in the lungs of patients with SLE.

The significant elevation of LDH during episodes of SLE in patients with either pleuritis or interstitial pneumonia indicates that this parameter is useful in the management of these pulmonary conditions. Although the mechanism underlying the elevation of serum LDH during episodes of these pulmonary complications is not clear, it is possible that LDH might be released from damaged inflammatory or parenchymal cells surrounding the lesion (16). There is also in vitro evidence of LDH leakage from type II pneumocytes, pulmonary endothelial cells and alveolar macrophages, following a number of insults such as hypoxia. The significant elevation of TM during disease episodes in SLE patients with pleuritis indicates that measurement of this variable would be useful in the management of these patients. TM levels did not rise in patients with interstitial pneumonia, suggesting that damage to vascular endothelial cells may not be involved in this condition. The increase in TM levels during pleuritic episodes might be caused by its release from damaged vascular endothelial cells. The TM molecule consists of fragments with various molecular weights which are probably degraded proteolytically from cellular TM, or may be derived from the injured and/or inflamed endothelial cells (17).

Abnormalities in pulmonary function tests, such as decreased DLCO and restrictive changes, were also common regardless of apparent presence of pulmonary involvement. It has been reported that weakness of the diaphragm and other respiratory muscles is an important feature in at least 25% of SLE patients (18,19). As to the frequencies of the pulmonary function abnormality in SLE, the restrictive change was found in 24 of 78 (28%) patients and the reduction in diffusing capacity was found in 32 of 74 (43%) patients in our study. These frequencies were almost comparable with those reported in previous reports (i.e. restrictive change: 10–49%; decreased DLCO: 31–94%), although backgrounds of patients in these reports were widely diverse in terms of the complication of the pulmonary disease (20–23). As to the clinical and laboratory correlates of the pulmonary function abnormality, we found that the restrictive change is associated with a positive LE test and elevated ESR and the decreased DLCO is relevant to Raynaud’s phenomenon, decreased Ccr, proteinuria, leukopenia and lymphopenia. The correlation of the restrictive change with positive LE test and elevated ESR may be
interstitial pneumonia suggests the possible significance of complication. Autoantibodies against SS-A in the pathogenesis of this frequencies of anti-SS-A antibodies in lupus patients who have involvement or a specific serological pattern and respiratory function abnormalities.

In conclusion, the increase in the levels of ESR, CRP, TM and WBC counts during episodes suggests the involvement of inflammatory processes related to vascular events in the pathogenesis of lupus pleuritis. The higher frequencies of anti-SS-A antibodies in lupus patients who have interstitial pneumonia suggests the possible significance of autoantibodies against SS-A in the pathogenesis of this complication.

References