The incidence and clinical characteristics of Mycobacterium tuberculosis infection among systemic lupus erythematosus and rheumatoid arthritis patients in Korea


The Hospital for Rheumatic Diseases, Department of Internal Medicine, Hanyang University College of Medicine, Seoul, South Korea

Abstract

Objectives
The aim of this study was to describe the incidence and clinical characteristics of Mycobacterium tuberculosis infection in SLE and RA patients in Korea where the prevalence rate of active pulmonary tuberculosis in a general population is relatively higher than in Western countries.

Patients
We reviewed the medical records of 283 SLE and 284 RA patients retrospectively and then assessed the incidence, risk factors, and clinical characteristics of active tuberculous infection. We then compared the results for the two different groups.

Results
Tuberculosis was documented in 15 SLE and 7 RA patients with an incidence rate of 7.9/1,000 patient-years and 2.3/1,000 patient-years, respectively (p = 0.003). SLE-associated tuberculosis cases included 3 of miliary tuberculosis, 7 of pulmonary tuberculosis (including 1 case of diffuse pulmonary involvement with meningitis) predominantly involving two or more lobes at the mid-/lower lung field, and 5 extra-pulmonary forms (joint, bone, kidney, larynx, pleura). All of the RA-associated tuberculosis cases were pulmonary forms with the majority being localized to single lobe, and only one case had a past history of tuberculosis, whereas a past history of tuberculosis and a longer duration of the underlying disease were significantly correlated with the development of tuberculosis in the SLE patients. Major organ involvement, the mean daily dosage of prednisolone, and a history of over 30 mg of daily prednisolone were not related to the development of tuberculosis. However, when we took only those patients taking corticosteroid until the diagnosis of tuberculosis for analysis, SLE patients with tuberculosis showed a higher daily dosage of prednisolone than those without tuberculosis.

Conclusion
Taken together, the characteristics of tuberculosis in SLE patients were: (1) a higher incidence rate, (2) more frequent extra-pulmonary involvement, (3) more extensive pulmonary involvement, and (4) a higher relapse rate than in rheumatoid arthritis. Thus, the contributory role of M. tuberculosis infection in the morbidity and mortality of patients with SLE must be emphasized, especially in areas in which this bacteria is endemic.

Key words
Systemic lupus erythematosus, rheumatoid arthritis, Mycobacterium tuberculosis infection.

Introduction
Infection is a major cause of morbidity and mortality in patients with rheumatic diseases including systemic lupus erythematosus (SLE) (1). Common bacterial pathogens are the most common causes of infection in SLE patients (2). Mycobacterium tuberculosis infection is an important cause of morbidity and mortality in patients with rheumatic disease, especially in prevalent areas (3, 4). According to a longitudinal epidemiological study carried out by the Korean Institute of Tuberculosis in 1995, the prevalence rate of active pulmonary tuberculosis evidenced by chest x-ray was estimated to be 1.03%, and this was especially higher in young people (5, 6). To date there have been several reports on the characteristics of tuberculosis infection in SLE patients (7-9), but few studies comparing SLE with other rheumatic diseases that are associated with tuberculosis. Here we investigated and analyzed the incidence rate and clinical characteristics of Mycobacterium tuberculosis infection in SLE patients and compared them with those of rheumatoid arthritis (RA) patients.

Patients and methods
We retrospectively reviewed the medical records of 283 consecutive SLE patients and 284 randomly selected RA patients (using a random-numbers table), who had been followed during the period March 1979 to February 2000. The patients enrolled fulfilled the 1982 American College of Rheumatology (ACR) revised criteria for SLE (10) and the 1987 ACR revised criteria for RA (11), respectively. We recorded the demographic characteristics such as sex, age, past history of tuberculosis, and onset age of rheumatic disease. The following clinical features were collected for the SLE patients: 1) chest x-ray findings at the first visit; 2) clinical manifestations such as malar rash, photosensitivity, oral ulcer, Raynaud’s phenomenon, arthritis, and serositis; 3) laboratory findings such as cytopenia(s), ANA titer, anti-ds DNA titer, complement level, and antiphospholipid antibody titer; 4) involvement of major organs such as the kidney or central nervous system (CNS); 5) development of infection caused by virus, bacteria, or fungus; and 6) the dosage and duration of corticosteroid and/or other immunosuppressants such as azathioprine, cyclophosphamide, or cyclosporine prior to the diagnosis of tuberculosis.

For the RA patients, the following data were collected; chest x-ray findings at the first visit and the dosages of corticosteroid and disease modifying anti-rheumatic drugs (DMARDs) administered prior to the development of tuberculosis.

The following tuberculosis data were collected: 1) a history of contact with active tuberculosis patients (particularly in family members) at least 2 years prior to the time of infection; 2) infected site(s); 3) chest x-ray findings; 4) mean daily and cumulative dose of prednisolone (or equivalent) up to the diagnosis of tuberculosis; 5) the time elapsed between the first symptom of SLE (defined according to the 1982 ACR revised criteria for SLE) or RA (synovitis) and the diagnosis of tuberculosis, and 6) the outcome of tuberculosis.

M. tuberculosis infection was defined as the newly developed symptoms and/or signs associated with one of the following results: 1) identification of acid-fast organisms by specimen smear, culture and/or polymerase chain reaction (PCR); 2) typical histological findings at the involved site; or 3) typical chest x-ray findings which improved after anti-tuberculosis treatment. We did not take into account the PPD skin test due to the mandatory BCG vaccination plan carried out in almost every region of Korea. The past history of tuberculosis was defined either as a history of pharmacologic treatment against tuberculosis for at least 1 year prior to the diagnosis of rheumatic disease or as an abnormal chest x-ray finding such as fibrostreaky density and/or calcific nodules suggesting past pulmonary tuberculosis infection.

Chest x-ray findings were classified as follows: normal, fibrostreaky density or calcific nodules, patchy infiltration or nodular density, cavitary lesion, pneumonic infiltration or consolidation.
Table I. Clinical characteristics of patients studied.

<table>
<thead>
<tr>
<th></th>
<th>Tuberculosis</th>
<th>Non-tuberculosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SLE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>15</td>
<td>268</td>
</tr>
<tr>
<td>Sex (Male : Female)</td>
<td>2 : 13</td>
<td>13 : 255</td>
</tr>
<tr>
<td>Mean age</td>
<td>38.3±11.7</td>
<td>35.9±12.3</td>
</tr>
<tr>
<td>Age at the diagnosis of SLE</td>
<td>32.9±11.7</td>
<td>31.8±12.1</td>
</tr>
<tr>
<td>Disease duration (years)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past history of tuberculosis (no)*</td>
<td>9.0 (3.0-26.0)</td>
<td>6.0 (1.0-28.0)</td>
</tr>
<tr>
<td>Joint</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>7</td>
<td>277</td>
</tr>
<tr>
<td>Sex (Male : Female)</td>
<td>2 : 5</td>
<td>40 : 237</td>
</tr>
<tr>
<td>Median age</td>
<td>53.0 (17.0-69.0)</td>
<td>53.0 (15.0-85.0)</td>
</tr>
<tr>
<td>Onset age</td>
<td>39.7±17.2</td>
<td>40.8±13.5</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past history of tuberculosis (no.)</td>
<td>1 (14.3%)</td>
<td>41 (14.8%)</td>
</tr>
</tbody>
</table>

* p < 0.05

Statistical analysis
Between the tubercular and non-tubercular groups, the continuous variables including demographic data, and the daily and cumulative prednisolone doses were compared using the Student’s t-test or the Mann-Whitney U test. The Chi-square test was also used to evaluate the association between tuberculosis infection and the individual clinical manifestations, major organ involvement, other infection, or immunosuppressive therapy. The incidence of tuberculosis infection in SLE patients was compared with that of the RA patients using the z-distribution. A probability of 0.05 was used to reject the null hypothesis that there was no difference between the 2 groups. Analysis was carried out using SPSS software (v. 8.0 for windows).

Results
Clinical characteristics
The basic demographic characteristics of the SLE patients are shown in Table I. The mean age of the patients was 36.1 years. Tuberculosis was documented in 14 SLE patients, and one patient relapsed 18 months after the treatment. The mean disease duration of these patients was 9 years, which was significantly longer than that of the SLE patients without tuberculosis (p < 0.05). Among the patients with tuberculosis, 5 (33.3%) had a past history of tuberculosis, a significantly higher frequency than the 10.8% in the patient group who did not develop tuberculosis (p < 0.05). None of the patients had a history of contact with active tuberculosis patients among their family members. There was no difference in the sex ratio, mean age, age at onset or age at the diagnosis of SLE between tubercular and non-tubercular patients. Also, there was no significant difference in the presence of various clinical manifestations, abnormal laboratory findings, involvement of the kidney or CNS, and other infection(s) between the 2 groups. Disease activity using the SLE Disease Activity Index (SLEDAI) (12) was measured at the diagnosis of RA; 7.9/1,000 patient-years versus 2.3/1,000 patient-years respectively (p-value = 0.003). Table I also shows the general characteristics of the 284 RA patients. Tuberculosis developed in 7 patients (2.5%) and a past history of tuberculosis before the diagnosis of RA was found in only one patient (14.3%) in the tuberculosis group, and in 41 patients (14.5%) in the non-tuberculosis group. Among the RA patients, there was no significant difference in the sex ratio, onset age, disease duration, or frequency of a past history of infection between the groups with and without tuberculosis.

The incidence rate and infected sites of tuberculosis
Tuberculosis developed in 15 cases among 283 SLE patients and in 7 out of 284 RA patients, and the incidence rate in SLE was significantly higher than that in RA; 7.9/1,000 patient-years versus 2.3/1,000 patient-years (p = 0.003) (Fig. 1). Among the 15 occurrences of tuberculosis in SLE patients, 12 revealed pulmonary involvement: 6 had disease limited to the lung, 3 had a miliary pattern, and 3 had both pulmonary and joint, meninges, or pleura involvement. The other sites were the kidney, larynx, and bone without lung disease. Among the RA patients, all 7 had pulmonary disease only (Table II). In the SLE patients, acid-fast bacilli were identified in all except 3, diagnosed on the basis of typical histologic findings, typical radiographic findings, or a miliary pattern of tuberculosis. Among the RA patients, one was diagnosed based...
Table III. Radiographic findings of tuberculosis.

<table>
<thead>
<tr>
<th>Extent of lung involvement</th>
<th>SLE (n=15)</th>
<th>RA (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miliary or diffuse</td>
<td>4 (26.7%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>One lobe</td>
<td>2 (13.3%)*</td>
<td>4 (57.1%)</td>
</tr>
<tr>
<td>Two lobes and more</td>
<td>6 (40.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Endobronchial tuberculosis</td>
<td>0 (0.0%)</td>
<td>1 (14.3%)</td>
</tr>
<tr>
<td>No significant interval changes</td>
<td>3 (20.0%)</td>
<td>2 (28.6%)†</td>
</tr>
<tr>
<td>Chest x-ray patterns</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miliary pattern</td>
<td>3 (20.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Patchy infiltration or nodular density</td>
<td>2 (13.3%)*</td>
<td>1 (14.3%)</td>
</tr>
<tr>
<td>Pneumonic infiltration or consolidation</td>
<td>6 (40.0%)</td>
<td>2 (28.6%)</td>
</tr>
<tr>
<td>Cavitary lesion</td>
<td>1 (6.7%)</td>
<td>1 (14.3%)</td>
</tr>
<tr>
<td>Negative finding</td>
<td>3 (20.0%)</td>
<td>3 (42.9%)‡</td>
</tr>
</tbody>
</table>

* One patient had pulmonary tuberculosis with tuberculous arthritis, and the other had pulmonary tuberculosis with pleural effusion suspected by tuberculous origin; † Both the patients had underlying interstitial lung disease without interval changes radiologically; ‡ One of them had endobronchial tuberculosis.

Radiographic extent and pattern of lung involvement on chest x-ray

Table III shows that 10 SLE cases (66.7%) had extensive pulmonary involvement, such as miliary tuberculosis or the involvement of 2 or more lobes. Only 2 patients (16.7%) with pleurisy or arthritis had limited infiltration confined to a single lobe on chest x-ray. Eleven patients showed abnormal findings in the middle or lower lobes irrespective of upper lobe involvement. Regarding the radiographic pattern in SLE patients, a miliary distribution and pneumonic infiltration were more common than patchy infiltration, nodular density or cavitary lesion (Table III). Among 7 RA, 4 (57.1%) were revealed to have typical radiologic findings localized to one lobe. One of the 7 RA patients, who turned later out to have endobronchial tuberculosis, showed a normal chest x-ray finding. Two RA patients with acid-fast bacilli documented by sputum smear, presented with fever and productive cough and showed underlying interstitial fibrosis without a definite interval change on chest x-ray.

Immunosuppressive therapy in SLE

The mean daily dosage of prednisolone was 15.9 mg in cases complicated with tuberculosis, and was not significantly higher than 8.4 mg in patients without tuberculosis (p = 0.2). Among the SLE patients with tuberculosis, 3 patients had not taken corticosteroid for at least 1 month before the diagnosis of tuberculosis, and 2 of these 3 patients have never been prescribed corticosteroid. When the subgroup of only those patients taking steroid were evaluated, the mean daily dosage of corticosteroid in cases complicated with tuberculosis was 19.9 mg, which was significantly higher than the 9.2 mg in the non-tubercular patients taking corticosteroid (p=0.01). One patient, who eventually died of miliary tuberculosis, received methylprednisolone (500 mg) pulse therapy twice within 1 month prior to the confirmation of tuberculosis. A history of prednisolone dosages of more than 30 mg/day for more than a month was documented in 57.1% of the tuberculosis patients and in 38.4% of the patients without tuberculosis; this difference was not statistically significant.

The relationship between other immunosuppressive drugs and tuberculosis was analyzed, but we could not find any significant difference between the two groups. However, the number of patients receiving immunosuppressive agents within one month of the diagnosis of tuberculosis was too small to make the interpretation of this data valuable.

Discussion

SLE is primarily a disease with abnormalities in immune regulation. Besides immunosuppressive therapy, immunological abnormalities such as impaired phagocytosis or deficiency of cell-mediated immunity may contribute to the increased risk of infection in SLE patients (13-16). Tuberculosis in SLE patients has been reported with a prevalence rate of 3.6% - 5.0% which is higher than in the general population (7, 8). It has been widely accepted that patients with impaired T cell function are at increased risk of developing clinically manifested tuberculosis (17-19). Furthermore, it has long been established that successful elimination of the intracellular tuberculous organisms from the host depends mainly on the efficient interaction between infected macrophages and antigen-specific T cells. However, there is increasing evidence that a major role exists for CD8+ T cells as well as CD4+ T cells in cellular immunity (20-23).

In our study, the incidence rate of tuberculosis was significantly higher in SLE patients than in RA. Compared with RA patients, SLE patients with tuberculosis showed a tendency of more frequent extra-pulmonary involvement and miliary or extensive pulmonary involvement of more than 2 lobes. In this regard, our findings were similar to those reported by Feng et al. (7). Although patients with RA also have displayed some evidence of impaired cell-mediated immunity (24-27), our data suggest that the impairment of cell-mediated immunity could be more extensive and serious in SLE than in RA. Actually, there have been a few reports showing greater impairment in the delayed hypersensitivity response, and a greater generation of anti-CD3-induced cytotoxic T lymphocyte in SLE than in RA patients or normal controls (28, 29).

Rovensky et al. (8) described 14 patients with SLE and tuberculosis. Four had septic fever to which glucocorticoid treatment did not respond, and 2 out of 3 miliary tuberculosis patients died despite anti-mycobacterial treatment. In our study, 2 of 3 miliary tuberculosis patients died due to treatment-
resistant tuberculosis accompanied by increased lupus activity. Two patients had symptoms and signs of active SLE such as fever, malar rash, arthritis, leukopenia, thrombocytopenia, high anti-DS DNA titers, and hypocomplementemia, and were treated with corticosteroid (prednisolone ≥ 30 mg daily). Afterwards they developed miliary tuberculosis presenting with fever, which can be confused with uncontrolled primary disease, and died after a rapid deterioration despite combination chemotherapy against tuberculosis. However, all 7 RA patients with pulmonary tuberculosis were well controlled with combination anti-tuberculous chemotherapy. Thus, we suggest that when SLE patients have fever responding poorly to corticosteroid, the possibility of tuberculous infection should always be considered, especially in the areas where tuberculosis is endemic. Furthermore, patients whose SLE is complicated by tuberculosis will tend to have a worse prognosis and should be treated promptly and aggressively with combination chemotherapy.

Long-term immunosuppressive therapy including corticosteroid may predispose to active tuberculosis (17, 30, 31). It has been well established that corticosteroids modify the cell-mediated immune response. Tuberculin reactivity is reduced after the patient receives prednisone > 15 mg/day (or its equivalent) for 2-3 weeks; this probably represents the lower limit of the corticosteroid dosage associated with an increased risk of tuberculosis (30). Millar and Horne described 11 patients who developed tuberculosis while receiving more than 10 mg of long-term prednisone daily or its equivalent for various underlying conditions (31). Kim et al. reported that the levels of steroid pulse therapy, and the cumulative and mean daily steroid dose were significantly higher in the tuberculosis than in the non-tuberculosis group (4). This result is contrary to a previous study showing similar tuberculosis prevalence rates in the normal population and asthma patients treated with steroids (32). In another study involving SLE patients only, active tuberculosis occurred not only in the patients who were administered high doses of glucocorticoid, but also in the patients who received a maintenance dose (10-15 mg of prednisolone) (8). In our study, when SLE patients taking corticosteroid were analyzed, the mean daily dosage of prednisolone was significantly higher in the patients with tuberculosis than in those without tuberculosis. It is suggested that a well-designed prospective study will be necessary to understand how glucocorticoid induces increased vulnerability to tuberculosis in an immune-dysregulatory condition such as SLE.

In SLE patients complicated with pulmonary tuberculosis, chest x-ray findings have been reported as developing in the middle or lower lung, with a high prevalence of milia r y dissemination and patchy consolidation, but rare cavity lesions (3, 9). Our pulmonary tuberculosis cases also had a tendency to involve 2 or more lobes, and to be more prevalent in the middle or lower lobes. Caseating necrosis, the hallmark of tuberculous granulomas resulting from a cell-mediated response by macrophages and lymphocytes, leads to the destruction of lung tissue with cavity formation. Thus, defective cell-mediated immunity in SLE might play a role in the decreased frequency of cavity formation by pulmonary tuberculosis in this patient group (9).

It is known that *M. tuberculosis* infects 25-30% of subjects who come into close contact with smear positive patients (33, 34). However, clinically active tuberculosis develops in only 10% of these infected persons. Approximately half of the clinically active subjects are reported to develop tuberculosis within 2 to 3 years from the time of infection, and the remainder may develop the disease at any time during the rest of their life. A detailed past history of tuberculosis was included in the study since the latent infection rate is reported to be relatively high in the Korean group aged over 20 (4). Among our SLE patients with a past history of tuberculosis before the development of SLE, 15.2% of the subjects (5 out of 33) had a relapse of tuberculosis and this was comparatively higher than the 2.4% in the RA patients (1 out of 42). Thus, this patient group should be closely observed for the possibility of tuberculosis reactivation. Of these 5 patients, 2 relapsed into a military pattern and one relapsed into meningitis with whole lung involvement.

In conclusion, the characteristics of tuberculosis in SLE patients are a higher incidence rate, more frequent and more extensive extra-pulmonary involvement, and a higher relapse rate than in RA patients. Thus, the prevention and early diagnosis of tuberculosis should be emphasized in SLE patients due to the substantial contribution of *M. tuberculosis* infection to morbidity and mortality, especially in areas endemic for *M. tuberculosis*.

**References**

12. LIANG MH, SOCHER SA, LARSON MG, SCHUR PH: Reliability and validity of six sys-
Tuberculosis in SLE and RA patients / J-E Yun et al.