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ORIGINAL ARTICLE

Tuberculosis infection in patients with systemic lupus erythematosus: pulmonary and extra-pulmonary infection compared

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Abstract Systemic lupus erythematosus (SLE) patients had an increased susceptibility to tuberculosis (TB). The aim of this study was to investigate the prevalence and clinical characteristics of TB in SLE patients, with focus on the differences between pulmonary and extra-pulmonary TB. This is a retrospective study that reviewed the medical records of 3,179 SLE patients from 1985 to 2004. The diagnosis of TB was confirmed by one of the following: positive acid-fast bacillus (AFB) smear, positive culture of *Mycobacterium tuberculosis* from appropriate specimens, or a histopathologic finding of caseating granuloma on specimen. During the 20-year review period, TB was documented in 19 SLE patients, with 21 episodes. Ten of 21 episodes (47.6%) were pulmonary TB while the other 11 episodes (52.4%) were extra-pulmonary TB. Among extra-pulmonary TB, there were joint and cutaneous involvements in five, miliary in two, Pott's disease in two, peritoneum in one, and spleen in one. The most common manifestations of TB were fever and cough. Delayed diagnosis and adverse effects of anti-TB therapy were observed in the extra-pulmonary TB group. While SLE patients commonly present with prolonged fever or chronic cough, tuberculosis infection should be taken into consideration.

Keywords Extra-pulmonary tuberculosis · Pulmonary tuberculosis · Systemic lupus erythematosus

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Introduction

Systemic lupus erythematosus (SLE) is a rheumatic disease of unknown cause and is characterized by autoantibodies directed against self-antigens that result in inflammatory damage to target organs, including the kidneys, blood cells, and the central nervous system (CNS). Major causes of death in patients with SLE include infection, renal failure, CNS disease, and myocardial infarction. With early meticulous diagnosis and treatment, there has been a significant increase in survival rate.

However, infection still plays an important role in the mortality and morbidity of SLE patients [1–4]. Although the majority of infections are due to Gram-positive or Gram-negative bacteria, there is increasing evidence indicating that opportunistic infections, such as candidiasis, cryptococcal meningitis, pneumocystis carinii pneumonia, invasive aspergillosis, and tuberculosis (TB), lead to mortality [5, 6]. Previous studies found that there was an increasing prevalence of TB infection in SLE, especially in endemic areas such as countries in the far east [7–10]. The high frequency and unusual spectrum of infections can be attributed to the multiple abnormalities of immune function in combination with the effects of immunosuppressive therapy. High doses of corticosteroids are implicated as a risk factor for infection [11–14].

However, the differences between pulmonary and extra-pulmonary TB were seldom discussed, especially from the

point of view of both of clinical characteristics and laboratory data. The aim of this study was to investigate the prevalence and clinical characteristics of TB in SLE patients, the differences between pulmonary and extra-pulmonary TB, and the risk factors of developing TB in SLE patients.

Materials and methods

We retrospectively reviewed the medical records of SLE patients with proven TB infection who had visited the Chang Gung Memorial Hospital and Children's Hospital from 1985 to 2004. All of the patients fulfilled the 1982 revised American Rheumatism Association criteria for the classification of SLE [15]. SLE disease activity was calculated according to the SLE Disease Activity Index (SLEDAI) [16]. The definite diagnosis of TB was confirmed by clinical manifestations and by one of the following: a positive acid-fast bacillus (AFB) smear, a positive culture of *Mycobacterium tuberculosis* from an appropriate specimen, or a histopathologic finding of caseating granuloma on specimens [7].

The demographic features and clinical characteristics collected from the medical charts included the patient's age, gender, the presence of CNS lupus or lupus nephritis, SLE disease activity (SLEDAI), duration between SLE diagnosis and TB diagnosis, interval between TB onset and diagnosis, TB location, clinical manifestations of TB, cumulative dose of prednisolone, therapeutic regimens and duration, and adverse effects and outcome of anti-TB therapy.

The patients were divided into two groups: pulmonary TB and extra-pulmonary TB. The demographic features, laboratory data, treatment, and prognosis of these two groups were compared and analyzed. We used chi-squared test, Fisher's exact test, Mann–Whitney *U* test, and Student's *t* test for comparison. Results were shown as a proportion or mean (standard deviation). A p value of 0.05 or less was considered statistically significant.

Results

From our medical records, there were 3,179 patients with SLE, in which there were 19 patients with 21 proven tuberculosis infections during the 20-year review period. Table 1 shows the demographic features of the SLE patients. The female to male ratio was 16:3. All of the patients were adults (mean age, 48.7±14.6 years). The average age for SLE diagnosis was 39.9 years old (SD= 16.7). Lupus nephritis was found in seven patients and CNS lupus in one.

The spectrum of tuberculosis is demonstrated in Table 2. The age at TB diagnosis ranged from 17.6 to 67.8 years old (mean, 45.0±14.9 years). There were 21 TB infection episodes documented among 19 patients during the 20-year

Table 1 Demographic features of SLE

Case	Sex	Age	Age at SLE diagnosis	Lupus nephritis	CNS lupus	Initial dosage of prednisolone (mg/day)	Other immuno-suppressives
1	F	64.3	59.6	+		50.0	H
2	F	69.1	66.8	+		30.0	
3	F	46.0	30.3	+		45.0	
4	F	26.4	19.7			10.0	H
5	F	48.3	45.1			60.0	
6	F	34.6	25.9	+		20.0	
7	F	37.4	28.5			5.0	H
8	F	51.0	38.4			10.0	H
9	M	52.6	50.1	+		14.3	E
10	M	61.6	54.9		+	100.0	
11	F	51.3	40.8			50.0	
12	F	64.1	57.7			45.0	
13	F	22.1	17.0			10.0	
14	M	28.3	11.7	+		45.0	A
15	F	42.9	34.4	+		30.0	E, A, H
16	F	64.5	58.2			10.0	H
17	F	48.4	39.4			60.0	H
18	F	70.5	58.8			20.0	
19	F	41.9	21.4			–[a]	H

F Female, *M* male; *CNS* central nervous system; *A* azathioprine, *E* cyclophosphamide, *H* hydroxychloroquine
[a] Data were missed due to initial treatment at other hospital

Table 2 Spectrum of tuberculosis

Case	Age at TB diagnosis	Predominant site of TB	Clinical symptoms	Interval between SLE and TB diagnosis (months)	Interval between TB onset and diagnosis (days)	Smear (AFB)	Culture	Histology
1	61.2	Lung	Fever, cough, sputum, dyspnea	19.2	28	N	+	
2	67.8	Lung	Cough, dyspnea, chest pain, BW loss, malaise	12.4	21	P	+	+
3	43.4	Lung	Cough, sputum, dyspnea, chest pain, BW loss, malaise	158.9	25	N	+	+
4	21.2	Lung	Fever, cough, sputum, dyspnea, chest pain, LAP	18.4	60	N	+	
5	45.6	Lung	BW loss, malaise	5.7	45	P	+	
6	29.5	Lung	Fever, cough, sputum, dyspnea, chest pain, orthopnea	43.7	22	P		
7	34.9	Lung	Cough, sputum, dyspnea, palpitation	77.1	60	P		
8	49.5	Lung	Fever, cough, sputum	134.9	30	N	+	
9	50.4	Lung	Fever, cough, sputum, dyspnea	3.5	30	P	+	
10	55.5	Miliary	Fever, cough, dyspnea	6.4	21	P	+	
11	42.0	Lung	Fever, cough, sputum, chest pain	15.1	60	P	+	
12	58.2	Skin	Finger nodule with pus and gangrene formation	5.6	150	P	+	
13	17.6	Peritoneum	Fever, cough, sputum, BW loss, abdominal pain, vomiting, diarrhea	8.2	35	P		
14	24.8	Knee	Knee swelling, arthralgia	159.3	21	P		
15	40.0	Miliary	Fever, cough, dyspnea, malaise	64.6	21	P	+	
	41.0	Hip	Right hip pain, cough	76.3	360	P	+	
16	60.4	Finger (PIP)	Fever, cough, sputum, left PIPs swollen/reddish	27.0	180	P	+	
	62.0	Skin	Fever, cough, subcutaneous nodules over left elbow and right forearm	46.3	30	N	+	+
17	47.7	Spleen	Fever, cough, sputum, jaundice	100.8	21	P		
18	66.8	Spine	Bilateral leg pain/ numbness, low back pain	97.4	180	N	+	+
19	38.4	Spine	Low back pain, claudication	206.5	300	P	+	

N Negative, *P* positive; *PIP* proximal interphalangeal, *BW* body weight, *LAP* lymphadenopathy, *AFB* acid-fast bacillus

review period. Ten of the 21 episodes (47.6%) had pulmonary TB, while the other 11 episodes (52.4%) were extra-pulmonary TB. Of the 11 extra-pulmonary TB cases, there were joint and cutaneous involvement in five, miliary in two, Pott's disease (vertebral bone tuberculosis) in two, peritoneum in one, and spleen in one. No patient had concomitant pulmonary and extra-pulmonary TB.

The most common manifestations of TB were cough (16/21, 76.2%) and fever (12/21, 57.1%). Other presentations included chest pain, dyspnea, body weight loss, night sweating, and arthralgia. The interval between the onset of SLE and TB diagnosis ranged from 3.5 to 206.5 months (mean, 60.8±60.8 months). The interval between TB onset and diagnosis ranged from 21 to 360 days (mean, 81.0± 97.5 days). The average cumulative dose and mean daily dose of prednisolone (since SLE diagnosis to TB diagnosis) were 37.7 g (SD=59.7) and 24.5 mg/day (SD=13.0), respectively.

All of the patients received anti-TB combination therapy with isoniazid, rifampin, ethambutol, pyrazinamide, streptomycin, or rifater (Table 3). The duration of anti-TB treatment ranged from 6.0 to 27 months (mean, 11.9± 6.7 months), except in cases 2 (4.5 months) and 8 (0.5 months) owing to loss of follow-up. There were two patients who had TB infection twice. Case 15 got miliary TB at the age of 40 years. She received anti-TB therapy right after TB diagnosis. Subsequently, due to intermittent right hip pain for 1 year, TB arthritis of the right hip joint was documented by culture of both the synovial fluid and hip soft tissue while she was under anti-TB therapy. She underwent girdlestone operation and implantation of antibiotic-loaded (streptomycin and vancomycin) prosthesis. Anti-TB therapy lasted for 14 months, and TB was cured but left some disability.

Case 16 had TB arthritis of the left proximal interphalangeal (PIP) joints at the age of 60.4 years. She had received anti-TB therapy for 6 months, and repeated culture of the joint aspirate revealed no growth of *M. tuberculosis*. However, subcutaneous nodules appeared over the left elbow and right forearm 1 year after the anti-TB therapy. Skin biopsy was done and disclosed caseating granulomatous inflammation with extensive caseous necrosis. Tissue culture yielded *M. tuberculosis*. We considered this episode relapsed TB infection, so anti-TB therapy was re-started and lasted for 12 months.

There were five patients (26.3%) that experienced adverse effects of the anti-TB drugs, including hepatotoxicity in two (case 10 and case 19), skin rashes in two (case 18 and case 19), visual disturbances in two (case 16 and case 18), and GI upset in one (case 15). Four patients required surgical intervention (cases 14, 15, 18, and 19). All of the patients were cured from those infections after anti-TB drugs therapy or surgery, except in one patient who was disabled (case 15) and two patients who were lost to follow-up (case 2 and case 8).

The patients were divided into two groups: pulmonary TB (n=10) and extra-pulmonary TB (n=11). Extra-pulmonary TB accounted for 52.4% of these TB infections. The sex ratio revealed a female predominance in both groups (Table 4). Eighteen (85.7%) patients had been taking prednisolone before the TB episode, and the mean daily dosage was 24.5 mg/day (SD=13.0). Nine patients (42.9%) had been taking other immunosuppressives or cytotoxic medications (azathioprine, hydroxychloroquine, or methotrexate).

No statistical difference was noted in the daily steroid dosage and in the usage of disease-modifying anti-rheumatic drugs (DMARD) between the two groups. There was no significant difference regarding age of TB diagnosis, cumulative dosage of prednisolone, duration between SLE and TB diagnosis, and SLEDAI. The interval between TB onset and diagnosis >60 days was significantly higher in the extra-pulmonary TB group compared to the pulmo-

Table 3 Result of anti-TB therapy

Case	Anti-TB regimens	Duration of TB treatment (months)	Adverse effect of TB treatment	Surgical intervention	Outcome
1	I,R,E,P	10.0			Cure
2	I,R,E	4.5			Loss of follow-up
3	I,R,E,P	9.0			Cure
4	I,R,E,P	6.0			Cure
5	Ri,E	24.0			Cure
6	I,R,E,P	27.0			Cure
7	I,R,E	18.0			Cure
8	I,R,E,P	0.5			Loss of follow-up
9	I,R,E,P	12.0			Cure
10	I,R,E,P,S	12.0	Hepatotoxicity		Cure
11	I,R,E	12.0			Cure
12	I,R,E,P	9.0			Cure
13	I,R,E,P	6.0			Cure
14	Ri,E	6.0		+	Cure
15	I,R,E,P	14.0	GI upset		Cure
	I,R,E	14.0	GI upset	+	Disability
16	I,R,E,P	6.0			Cure
	I,R,E	12.0	Visual disturbance		Cure
17	Ri,E	12.0			Cure
18	I,R,E,P	13.0	Visual disturbance, skin rash	+	Cure
19	I,R,E,P,S	23.0	Hepatotoxicity, skin rash	+	Cure

I Isoniazid, *R* Rifampin, *Ri* Rifater, *E* Ethambutol, *P* Pyrazinamide; *S* Streptomycin; *GI* gastrointestinal

Table 4 Clinical characteristics of patients with TB (pulmonary TB vs extra-pulmonary TB)

	Pulmonary TB (n=10)	Extrapulmonary TB (n=11)	*p* value
Sex (F/M)	9:1	9:2	1.000
Age at TB diagnosis	44.6 (13.9)	46.5 (15.9)	0.833
Lupus nephritis	5/10	3/10[a]	0.650
CNS lupus	0/10	1/10[a]	1.000
DMARD use when TB diagnosis	3/10	6/11	0.387
Cumulative dosage of prednisolone (g)	20.7 (19.7)	54.8 (80.5)	0.290
Mean daily dosage of prednisolone (mg/day)	21.3 (9.4)	27.8 (15.7)	0.305
Duration between SLE and TB diagnosis (months)	48.9 (56.3)	71.7 (65.4)	0.360
Interval between TB onset and diagnosis (days)	38.1 (16.5)	119.9 (123.5)	0.052
Interval between TB onset and diagnosis >60 days	0/10	5/11	0.035
SLEDAI	8.7 (5.8)	7.4 (3.4)	0.879

Result shown as proportion or mean (SD)
SD Standard deviation; *CNS* central nervous system; *DMARD* disease modifying anti-rheumatic drugs; *SLEDAI* SLE disease activity index
[a] Data were missed due to diagnosed at other hospital

nary TB group (p=0.035). Furthermore, the extra-pulmonary TB group tended to have adverse effects of anti-TB therapy (p=0.012), but the duration of anti-TB therapy did not differ significantly between the two groups (Table 5). The most common manifestations of tuberculosis were fever and cough for both groups.

The mean duration of anti-TB therapy was 11.9 months (SD=6.7), but there was no significant difference between the two groups. Four of the extra-pulmonary TB patients needed surgical intervention but none in the pulmonary TB group. Table 6 illustrates the laboratory data at the time of TB infection. A raised proportion of segment was found significantly higher in the pulmonary TB group (p=0.026).

Table 5 Clinical characteristics of patients with TB (cont.) (pulmonary TB vs extra-pulmonary TB)

	Pulmonary TB (n=10)	Extrapulmonary TB (n=11)	*p* value
Fever	6/10	6/11	1.000
Cough	9/10	7/11	0.311
Dyspnea	7/10	2/11	0.030
Chest pain	5/10	0/11	0.012
BW loss	3/10	1/11	0.311
LAP	1/10	0/11	0.476
Symptoms not associated with lung	1/10	10/11	0.000
Duration of anti-TB therapy (months)	12.3 (8.4)	11.5 (4.9)	0.831
Adverse effects of anti-TB therapy	0/10	6/11	0.012
Surgical intervention	0/10	4/11	0.090
Duration of hospitalization (days)	26.4 (16.6)	21.7 (11.8)	0.725

Result shown as proportion or mean (SD)
SD Standard deviation; *BW* body weight, *LAP* lymphadenopathy

Aside from this, there were no significant differences in laboratory data. Nevertheless, higher titers of antinuclear antibodies (ANA) and anti-dsDNA in the pulmonary TB group were observed. The severity of renal function

Table 6 Laboratory data of TB (pulmonary TB vs extra-pulmonary TB)

	Pulmonary TB (n=10)	Extrapulmonary TB (n=11)	*p* value
WBC (/μl)	7,840.0 (4,759.6)	8,036.4 (3,690.3)	0.622
Seg (%)	82.9 (11.2)	73.1 (10.4)	0.026
Lym (%)	9.7 (8.1)	12.8 (5.1)	0.161
Band (%)	1.4 (1.9)	2.6 (3.4)	0.544
Hb (g/dl)	10.0 (1.5)	10.3 (1.1)	0.832
Platelet ($\times 10^3$/μl)	219.7 (168.6)	274.5 (119.2)	0.260
C_3 (mg/dl)	85.0 (36.3)	90.4 (14.8)	0.806
C_4 (mg/dl)	16.1 (9.0)	23.3 (8.0)	0.086
Anti-ds DNA (IU/ml)	161.4 (424.9)	70.1 (65.5)	0.183
CRP (mg/l)	37.3 (23.1)	55.8 (60.6)	0.917
ESR (mm/hr)	63.8 (28.7)	55.0 (17.1)	1.000
Albumin (g/dl)	2.7 (0.6)	2.8 (0.6)	0.412
BUN (mg/dl)	20.9 (20.5)	19.6 (11.1)	0.705
Cr (mg/dl)	2.2 (2.4)	0.9 (0.4)	0.748
Cholesterol (mg/dl)	155.3 (18.8)	180.5 (55.0)	0.507
Triglyceride (mg/dl)	136.7 (73.2)	161.7 (14.5)	1.000
AST (U/l)	25.7 (9.6)	30.5 (14.9)	0.594
ALT (U/l)	18.4 (10.2)	46.5 (51.9)	0.074
Alk-P (U/l)	100.1 (51.7)	107.9 (66.7)	0.860
Protein (U) (mg/dl)	97.5 (153.4)	50.0 (48.6)	0.814
RBC (U) (/μl)	36.7 (81.7)	12.1 (17.8)	0.486
WBC (U) (/μl)	17.6 (31.3)	8.0 (6.2)	0.569

Result shown as mean (SD)
SD Standard deviation

impairment (elevated Cr level, proteinuria, and hematuria) was also noted much more in the pulmonary TB group. Eventually, all patients recovered after adequate anti-tuberculosis drugs therapy or operation except one patient disabled and two patients lost to follow-up.

Discussion

Tuberculosis is the world's second most common cause of death from infectious disease, after HIV/AIDS [17, 18]. According to the World Health Organization 2003 report, the estimated TB incidence and mortality were 140 and 28 cases per 100,000 population, respectively. The largest number of cases occurs in the South East Asia Region, which accounts for 33% of cases globally. As for Taiwan, the estimated TB incidence in 2004 was 105 cases per 100,000 population, based on the Center for Disease Control of Taiwan.

In Taiwan, TB infection still accounts for morbidity and mortality of SLE patients despite the low prevalence. In our study, there were 21 tuberculosis infections documented in 3,179 SLE patients, of which prevalence was about 0.66%. Previously, the prevalence of TB in SLE patients has been reported to be between 3.6 and 11.6% [7–9, 19–22]. The highest reported prevalence was from India [8]. Our prevalence was far less than those of previous studies. One reason is that our data was limited because of the structure of the cohort. Another reason is that the previous studies' populations included the lupus clinic. However, even this percentage might be an underestimation because patients who were lost to follow-up were not considered.

The most remarkable finding of this study is the increased incidence of extra-pulmonary location (52.4%) of TB in SLE patients. This proportion was high compared to patients with SLE from other countries [5, 7, 9, 10, 23, 24]. Furthermore, we found a significant delayed diagnosis >60 days (p= 0.035) and tendency to have adverse effects of anti-TB therapy (p=0.012) in the extra-pulmonary TB group compared to the pulmonary TB group. We thought extra-pulmonary TB mimicked other diseases, such as inflammatory arthritis, SLE pleurisy, or cellulitis, which was the major reason for the delayed diagnosis. Feng and Tan [9] considered a longer period to establish a definitive diagnosis in cases of extra-pulmonary infection because of the need for tissue examination. Our experiences disclosed that any persistent or prolonged fever, cough, sputum, dyspnea, joint swelling, arthralgia, or unexplained pulmonary infiltrates in SLE patients should be viewed with a high index of suspicion for tuberculosis.

On the other hand, there were six TB infection episodes with adverse effects of the anti-TB therapy, including hepatotoxicity, GI upset, visual disturbances, and skin rashes. All were extra-pulmonary TB cases, but the duration of anti-TB therapy did not differ significantly between the two groups. Small et al. described detailed adverse effects of anti-TB drugs [25]. No previous study or literature documented the same findings among SLE or other immuno-compromised patients. After changing anti-TB regimens, those adverse effects subsided and left no sequelae.

Ahmet. et al. retrospectively investigated and analyzed 636 non-SLE extra-pulmonary TB patients from 1996 to 2000 [26]. The most frequent form of extra-pulmonary TB was observed to be lymph node tuberculosis (56.3%). The second most frequent extra-pulmonary form was pleural tuberculosis (31.1%), followed by bone/joint TB, gastrointestinal TB, genitourinary TB, and cutaneous TB. Another study carried out in Canada and China also reported similar findings [27]. In our study regarding SLE patients, bone and joint TB was the most common extra-pulmonary TB (5/11, 45.5%), which is very different from non-SLE patients.

Some authors suggest that the treatment with high-dose corticosteroids or immuno-suppressive drugs may be a risk factor for the development of TB infection in patients with SLE [5, 7, 12, 19, 28]. We advanced found a higher cumulative dose and mean daily dose of prednisolone before TB infection in the extra-pulmonary TB group. Although there was no statistically significant difference between the pulmonary and extra-pulmonary groups, we should pay attention to the increasing possibility of developing extra-pulmonary TB in SLE patients who receive high dose corticosteroids.

Clinical symptoms and signs of TB were variable in SLE patients because SLE and TB share a large proportion of clinical manifestations, such as fever, cough, chest pain, malaise, body weight loss, or arthralgia, as well as similar laboratory data. This makes early diagnosis based on clinical presentation alone difficult, especially in patients with extra-pulmonary TB. Whenever TB is suspected, it is necessary to obtain sputum or tissue for AFB stain, culture for *M. tuberculosis*, and histology aside from chest radiography.

The goals of treatment are to ensure cure without relapse, prevent death, stop transmission, and prevent the emergence of drug resistance [17]. *M. tuberculosis* can remain dormant for long periods, so long-term treatment with a combination of drugs is required. Our patients all underwent combination therapy based on the WHO-recommended treatment regimens. The duration of anti-TB therapy depended on smear and culture conversions. Only the second TB episode of case 16 was considered a relapse because it was diagnosed 1 year after the anti-TB therapy and culture conversion. Finally, all of the patients were cured after surgery or the completion of anti-TB therapy, except for one patient who was disabled and two patients lost to follow-up.

In conclusion, we found a higher frequency of extrapulmonary TB in SLE patients despite the low prevalence of TB infection among SLE patients in Taiwan. The aim of this study was to highlight the importance of early suspicion and the struggle to diagnose and control tuberculosis. The use of oral and intravenous corticosteroids might be related to the disease severity and might further result in developing TB in these SLE patients. Whenever SLE patients present with prolonged fever, chronic cough, malaise, body weight loss, or arthralgia, TB infection should be taken into consideration. Once suspected, smear and culture of *M. tuberculosis* should be performed as soon as possible, as an accurate diagnosis and early intervention are crucial to cure.

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