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Tuberculosis in patients with systemic lupus erythematosus

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SUMMARY Tuberculosis associated with systemic lupus erythematosus (SLE) was studied in a cohort of 311 patients seen between 1963 to 1979. There were 16 such patients, giving rise to a prevalence rate of 5%. The characteristics of SLE-associated tuberculosis include a high incidence of miliary and far-advanced pulmonary disease, delay in establishing diagnosis, especially the extrapulmonary form, and tendency to attribute symptoms like fever, malaise, and weight loss to the lupus process. Treatment was successful in 9 patients. Of the 7 deaths 5 were attributed directly to the mycobacterial infection and 2 to complications of SLE.

In spite of an increased incidence of infection an association between tuberculosis and systemic lupus erythematosus (SLE) has been noted only infrequently.[1–3] The present report describes a systematic review of tuberculous infection in a cohort of 311 patients with SLE undergoing treatment with various immunosuppressive drugs over a period of 16 years from 1963 to 1979.

Materials and methods

PATIENTS

We reviewed the records of 311 patients diagnosed as SLE from 1963 to 1979. All these patients fulfilled at least 4 of the criteria laid down by the American Rheumatism Association.[4] The diagnosis of tuberculosis was made on radiological, bacteriological, and histological grounds.

EVALUATION OF DISEASE ACTIVITY

Clearly there are problems in defining disease activity in such a pleomorphic condition as SLE. Since renal status is one of the basic determinants of prognosis, we have adopted the system of Cameron *et al.*[5] (Table 1) to score disease activity arbitrarily. An added advantage of this system is that some weight is given to nonrenal manifestations as well as renal. Disease activity was expressed on a 7-point scale. A score of 1 or 2 was designated as mild disease and a score of 3–7 as moderate or severe disease.

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Table 1 *Assessment of disease activity*

	*Score**
Renal manifestations:	
Falling GFR/rising serum creatinine	2
Proteinuria present	1
Proteinuria but in excess 4 g/day or serum albumin <2·5 g/dl (25 g/l)	2
Sustained diastolic hypertension	1
Extrarenal manifestations:	
Mild	1
Severe	2

* Maximum possible score 7.
From Cameron *et al.*[5]
GFR = glomerular filtration rate.

THERAPY

Treatment of SLE was along standard lines. All patients received steroids initially at a dosage of prednisolone 60–20 mg a day depending on disease activity and specific organ involvement. The dosage was reduced gradually once the disease came under control. Cyclophosphamide was added at a dose of 1·5 mg/kg body weight in steroid failure or in those who developed severe steroid side effects. At the time of diagnosis of tuberculosis 15 of the patients were on prednisolone varying from 45 mg to 5 mg daily (mean daily dose 26 mg). Two of the patients received cyclophosphamide as well. One patient (case 7) was off drugs, as she was in remission.

For tuberculosis 8 patients received a combination of streptomycin (1 g daily), ethambutol (25 mg/kg body weight per day for first 8 weeks followed by 15 mg/kg body weight per day), and isoniazid (300 mg/day). Six patients received a combination

of streptomycin, para-aminosalicylic acid (10 g/day) and isoniazid. Two patients received a combination of rifampin (450 mg/day), ethambutol, and isoniazid. One patient developed skin sensitivity to streptomycin, and she was switched over to a combination of kanamycin (1 g 4 times a week), pyrazinamide (20–35 mg/kg), and rifampin. Case 16 did not respond to a combination of streptomycin, para-aminosalicylic and isoniazid and was changed over to rifampin, pyrazinamide, ethambutol, and ethionamide (250 mg thrice daily).

Results

CLINICAL FEATURES OF SLE

Detailed clinical features are presented in Table 2. All 16 patients had cutaneous and musculoskeletal involvement in the form of rash and arthritis. Nine patients had renal disease in the form of haematuria, nephrotic syndrome, and raised blood urea nitrogen or creatinine. Other systemic involvement included neuropsychiatric, respiratory, cardiac, haematological, or gastrointestinal manifestations.

SPECTRUM OF TUBERCULOSIS

This is shown in Table 3. Fever, cough, sputum, haemoptysis, dyspnoea, and weight loss were common in these patients but not invariably present. Some of these symptoms were initially attributed to the SLE itself.

Seven of the patients (44%) developed tuberculosis within the first 12 months of therapy for SLE. Nine patients (57%) developed tuberculosis within the first 2 years of therapy. With the exception of 1 case (no. 7) who had haemoptysis 2 years prior to development of active radiological lesion, diagnosis of tuberculosis was established within 3 months of onset of symptoms. This was done with radiology and/or sputum examination and culture in 14 cases. In case 5 the diagnosis was reached only at laparotomy, and in case 15 lymph node biopsy confirmed the diagnosis. In case 6 tuberculous osteomyelitis was confirmed by exploration of the left hip, though the chest radiograph also revealed a soft opacity suggestive of minimal tuberculosis.

RESULTS OF THERAPY

All patients were started on antituberculous therapy immediately on confirmation of diagnosis. All who completed chemotherapy had shown both radiological clearing and bacteriological conversion. Side effects of chemotherapy were infrequent and necessitated change of drug in only 1 patient (case 9). Of the 16 patients 7 died, giving a total mortality of 44%. Two patients died as result of complications of SLE, 1 of uraemia, and 1 of infection. Five patients (31%) died directly as result of tuberculosis. These patients had either very advanced cavitating pulmonary disease or miliary spread. Duration of treatment for this group varied from less than 1 month to 12 months.

EFFECT OF DISEASE ACTIVITY AND STEROID THERAPY

The number of tuberculous patients in relation to disease activity and steroid therapy is shown in Table 4. Eleven patients developed tuberculosis while their SLE was moderately severe or severe

Table 2 *Profile of patient population*

Case	*Age*	*Sex*	*SLE systemic manifestations*					*Initial therapy (mg/day)*
			Musculoskeletal	*Renal*	*Neuropsychiatric*	*Raised BP*	*Others*	
1	36	F	+	+	+	+	Thrombocytopenia, GIT	P 60
2	27	F	+				Pulmonary hypertension, heart block	P 60
3	38	F	+					P 15
4	54	M	+	+		+	Thrombocytopenia	P 45
5	23	F	+	+				P 45
								E 100
6	25	F	+					P 20
7	30	F	+	+				P 30
8	26	F	+			+	Lymphadenopathy	P 40
9	38	F	+	+	+	+		P 45
10	21	F	+	+	+			P 40
								E 100
11	17	F	+	+			Thrombocytopenia, ascites	P 30
12	28	F	+					P 30
13	63	F	+	+			Lung fibrosis	P 30
14	37	F	+					P 30
15	20	F	+	+				P 40
								E 100
16	55	F	+					P 30

P = prednisolone. E = cyclophosphamide (Endoxan). BP = blood pressure. GIT = gastrointestinal tract.

Table 3 *Spectrum of tuberculosis*

Case	*Clinical symptoms*	*Predominent site of infection*	*Positive diagnostic procedures*	*Therapy at time of diagnosis (mg/day)*	*Interval SLE→TB (months)*	*Delay in establishing diagnosis (months)*
1	Fever, cough, weight loss	Lung (far advanced)	*X*-ray, sputum	P 40	6	3
2	Cough	Lung (moderately advanced)	*X*-ray, sputum	P 40	3	1
3	Cough, weight loss	Lung (moderately advanced)	*X*-ray, sputum	P 7·5	72	1
4	Cough	Lung (moderately advanced)	*X*-ray, sputum	P 5	12	1
5	Fever, chills, ascites, LIF mass	Abdomen	Laparotomy	P 40	36	3
6	Pain and swelling left hip	Lung (minimal) TB hip	*X*-ray, surgical exploration	P 10	12	2
7	Haemoptysis	Lung (moderately advanced)	*X*-ray, sputum	—	124	24
8	Fever, cough, dyspnoea	Lung (miliary)	*X*-ray, sputum	P 45	30	1
9	Fever, chills	Lung (miliary)	*X*-ray, sputum	P 45	84	2
10	Fever, cough	Lung (far advanced)	*X*-ray, sputum	P 20+E	44	1
11	Cough	Pleural effusion	*X*-ray, pleural biopsy	P 15	9	1
12	Fever	Lung (miliary)	*X*-ray, sputum	P 30+E	9	2
13	Fever, chest pain	Lung (miliary)	*X*-ray	P 30	18	1
14	Fever, cough	Lung (miliary)	*X*-ray, sputum	P 15	7	1
15	Mass right clavicular fossa	Lymph node	Biopsy	P 15	33	2
16	Cough	Lung (far advanced)	*X*-ray, sputum	P 30	17	1

P = prednisolone. E = cyclophosphamide (Endoxan). LIF = left iliac fossa.

Table 4 *Result of therapy*

Case	*Disease score*	*Therapy of SLE (mg/day)*	*Therapy of tuberculosis*	*Duration of TB treatment (months)*	*Result*	*Associated condition/remarks*
1	3	P 40	Strept EMB INH	1	Died	
2	3	P 40	Strept EMB INH	2	Died	Lupus carditis
3	In remission	P 7·5	Rif EMB INH	12	Well	
4	2	P 5	Strept EMB INH	18	Well	
5	6	P 40	Strept EMB INH	24	Well	
6	1	P 10	Strept EMB INH	6	Well	
7	In remission	—	Strept EMB INH	18	Well	Thyrotoxicosis
8	3	P 45	Strept EMB INH	18	Well	Pregnancy
9	7	P 45	Strept EMB INH Kana PZA Rif	5	Well	Sensitive to strept
10	3	P 20+E 100	Rif EMB INH	18	TB improved Died of uraemia	
11	3	P 15	Strept PAS INH	10	TB improved Died of infection	
12	4	P 30+E 100	Strept PAS INH	10	Died	
13	4	P 30	Strept PAS INH	1 mth	Died	
14	2	P 15	Strept PAS INH	6	Improved	Lost to follow-up. Chronic schizophrenia
15	3	P 15	Strept PAS INH	18	Well	
16	3	P 30	Strept PAS INH Rif PZA EMB ETH	12	Died	Relapse TB

P = prednisolone. E = cyclophosphamide. Strept = streptomycin. PAS = Para-aminosalycilic acid.
EMB = ethambutol. INH = isoniazid. Rif = rifampin.
Kana = kanamycin. PZA = pyrazinamide. ETH = ethionamide.

(scale 3–7). Their steroid dosage varied from 15 to 45 mg per day (mean 32 mg). Two of them were on cyclophosphamide 100 mg/day as well. The type of tuberculosis in these 11 patients included 4 miliary, 4 pulmonary (3 far advanced and 1 moderately advanced), 1 abdominal, 1 lymphadenitis, and 1 pleural effusion. All the 7 deaths occurred in this group. The spectrum of tuberculosis in patients with mild SLE (on a scale of 1–2) or in remission were miliary in 1, pulmonary in 4 (1 minimal with TB osteomyelitis and 3 moderately advanced). There was no far advanced or cavitating disease in this group. Prednisolone dosage in this group ranged from 5 to 15 mg per day.

Discussion

The high incidence of serious infections is one of the

most disturbing problems in the management of patients with SLE. Besides immunosuppressive therapy several immunological abnormalities appear to contribute to the pathogenesis.[6–9] Hence such patients are at an increased risk of viral, mycotic, and other opportunistic infections.[10–13] The risk of specific tuberculous infection in immunosuppressed patients, however, has not been emphasised until very recently. Millar and Horne[14] reported 11 patients who developed tuberculosis while on long-term immunosuppressive therapy. Three of the patients died as a result of the disease. Sahn and Lakshminarayan[15] described 13 cases of tuberculosis in patients on corticosteroid therapy. All but one of them had an underlying condition associated with reduced immunity. Recently dialysis-associated tuberculosis has attracted considerable attention. Sasaki *et al.*[16] reported 12 tuberculosis patients out of 367 patients on maintenance haemodialysis in a survey from January 1967 to December 1976, giving an incidence of 3·3%. This was 6–16 times greater than that in the general population of Japan according to yearly statistics. Roughly similar results were obtained by Lundin *et al.*[17] and Rutsky and Rostand.[18]

On the other hand only sporadic reports of tuberculous infection in SLE patients have appeared. The general impression was that such an association was uncommon even in those treated with steroids and immunosuppressive drugs. We are unaware of any data analysing the relationship of SLE and tuberculosis. The relatively high prevalence in our patients suggests that physicians taking care of such patients should be aware of this potential hazard. This is especially true in geographical regions like Singapore where the incidence of new cases per year is around 3000 and there are probably twice the number of undiagnosed cases.[19] In spite of this heightened awareness the average interval between presentation and diagnosis was 1·5 months (range 1–3 months apart from case 7). In general, it took a longer period to establish definitive diagnosis in cases of extrapulmonary infection. This is due to the need for tissue examination. Our experience suggests that any prolonged febrile episodes, cough, sputum, dyspnoea, and weight loss should be viewed with suspicion. Unexplained pulmonary infiltrates, lymphadenopathy, pleural effusion, and ascites should be evaluated aggressively for active tuberculosis and not be attributed to the original disease. Severity of SLE and steroid dosage correlated positively with severity of tuberculosis and mortality. In individual patients with a clinical course compatible with tuberculosis, though lacking in histological or laboratory confirmation, a judicious trial of anti-mycobacterial drug therapy is probably indicated. Lastly a programme of assessment as recommended by Millar and Horne[14] for immunosuppressed patients at risk of developing tuberculosis is warranted if we are further to reduce the mortality and morbidity in this group of patients.

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