Mycobacterium tuberculosis infection in patients with systemic rheumatic diseases. A case-series

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Abstract

Objective

To describe the clinical characteristics of patients with systemic rheumatic diseases and tuberculosis. A retrospective case series from 1987 to 1994, drawn from a tertiary-care hospital in Mexico City, was studied.

Results

Thirty patients were included (20 women, 10 men), with mean age of 39.8 years (range 14 - 66), and a mean duration of the systemic rheumatic disease of 44 months (1 - 372). The rheumatic diseases included systemic lupus erythematosus (SLE) (n = 13), rheumatoid arthritis (7), polymyositis or dermatomyositis (5), and other diseases (5). During the six months previous to the diagnosis of tuberculosis, 22 patients had received corticosteroids, and 13 others immunosuppressants. Mycobacterium tuberculosis was isolated from 18 patients. Pulmonary tuberculosis was found in 10 patients, and extrapulmonary tuberculosis in 20, seven of these with miliary disease. SLE was seen in 6 of the patients with miliary tuberculosis. The clinical manifestations were: fever (67%), weight loss (67%), diaphoresis (60%), cough and sputum (53%), lymph node enlargement (43%), and dyspnea (33%). Sixteen patients had an abnormal chest film. Of 18 patients tested by PPD RT-2, 8 had an induration > 10 mm. Patients were initially treated with 3 or 4 anti-tuberculosis drugs for 15 days to 6 months, followed by 6 to 10 months of isoniazid plus rifampicin. Three relapsed, and 2 died of respiratory failure.

Conclusions

This case series showed a particular pattern of tuberculosis in patients with systemic rheumatic diseases.

Key words

Tuberculosis, systemic lupus erythematosus, systemic rheumatic diseases, developing countries.

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Introduction

A change in the prevalence and transmission of tuberculosis has been observed in recent years (1-3). In addition, the treatment of systemic rheumatic diseases includes better immunosuppressive agents, and patients with systemic rheumatic disease are more likely to survive longer (4). These patients have thus become more susceptible to infections (5), such as tuberculosis (6), either by the disease itself or its treatment, mainly steroids. This is particularly true in under-developed countries (7) with high rates of tuberculosis. In Mexico, an estimated 51.7 new cases of all forms of tuberculosis per 100,000 habitants was found in 1997 (8), and the incidence of tuberculosis in patients with systemic rheumatic disease was about 2.5% in 1994 (9).

Recently, patients with rheumatic diseases treated with corticosteroids in Korea showed an incidence rate of 20/1,000 patients-years of tuberculosis (10). The association of tuberculosis and systemic rheumatic diseases, particularly systemic lupus erythematosus (SLE) could potentially be life threatening (5-7, 11). The clinical manifestations of both systemic rheumatic disease activity and tuberculosis, (i.e. fever, weight loss, asthenia) may overlap or lead to confusion. The purpose of this study was to describe the clinical characteristics of tuberculosis in Mexican patients with systemic rheumatic diseases.

Materials and methods

The clinical records of all patients with a systemic rheumatic disease and concurrent tuberculosis seen at our clinic between 1987 and 1994 were reviewed. Cases were individuated based on: (a) the diagnostic records for in-patients at the time of discharge; b) all cases with a positive culture for *M. tuberculosis* and/or a positive Ziehl-Neelsen stain; and (c) the autopsy records of patients with tuberculosis.

The following variables were obtained from the medical records: (1) demographic data; (2) clinical characteristics of the systemic rheumatic disease; (3) treatment protocol (dosage and duration of steroids, chloroquine, and/or immunosuppressants), at any time during the course of the systemic rheumatic disease, as well as during the 6 months prior to the development of tuberculosis; and (4) the clinical manifestations, treatment, and outcome of the tuberculosis. Patients with AIDS, or a hypoadrenal state (defined as the presence of clinical manifestations and a low morning cortisol level, observed at least two times), or those who had been diagnosed with tuberculosis before the development of the systemic rheumatic disease were excluded. The degree of weight deficit was assessed in relation to the patient's ideal weight (12).

The criteria of the American College of Rheumatology were used to define the diagnosis of SLE (13), rheumatoid arthritis (RA) (14), Wegener's granulomatosis (15), Henoch-Schönlein purpura (16) and scleroderma (17). Polymyositis and dermatomyositis were diagnosed according to the criteria of Bohan and Peters (18), and mixed connective tissue disease (MCTD) according to Alarcón-Segovia's criteria (19). Active systemic rheumatic disease was defined as the presence of clinical manifestations observed on two consecutive occasions by the attending rheumatologist.

Tuberculosis was diagnosed based on the presence of clinical manifestations and one or more of the following criteria: a positive culture for *M. tuberculosis*; the presence of granulomas with caseous necrosis and Langhans giant cells on either tissue biopsy or post-mortem study; and the detection of mycobacterium by fluorochrome stain (auramine-rhodamine) and by acid fast stain (Ziehl-Neelsen) in the tissue biopsy or in respiratory samples (20). Urinary tuberculosis was diagnosed based only on a positive culture (21).

All samples were processed according to conventional techniques by decontamination with NAOH and N-acetyl-cysteine, inoculation onto Lowenstein-Jensen and Middlebrook 7H11 culture media, and incubation at 37°C for eight weeks in a CO_2-rich atmosphere. The susceptibility test was carried out using conventional techniques (22). PPD RT-23 (2U) was used to test the patients. An area of induration > 10 mm measured by the standard ball-point pen technique was considered as positive (23). A good response to anti-tuberculosis drugs was defined as the complete resolution of the

clinical symptoms and negative cultures during and after treatment.
Descriptive statistics were used and the results were expressed as percentages, median, and limits.

Results

Case 1

A 63-year-old female without a prior history of tuberculosis presented in 1962 with arthritis, fever, photosensitivity, malar rash, Raynaud's phenomenon, alopecia, and sicca syndrome with LE cells. She received steroids for 2 years, and remained asymptomatic for 34 years. In May 1992 she was admitted to the hospital, presenting with photosensitivity, malar rash, symmetric polyarthritis of the PIP, MCP, and wrist, fever and right deep vein femoral thrombosis. She was anemic (Hb = 8.4 g/dl), and had lymphopenia (700 lymphocytes/mm^3), double-stranded anti-DNA antibodies 47% (normal level < 35%), and an IgG anticardiolipin antibody titer of 2.2 U (normal level < 1.4 U).
SLE and secondary antiphospholipid syndrome were diagnosed and the patient was treated with prednisone (30 mg/day), isoniazid (300 mg per day for 6 months), and heparin followed by warfarine, with a good response. Prednisone was tapered over 6 months to 7.5 mg/day, and chloroquine 150 mg/day was added to the regimen. In February 1994 she relapsed with fever, arthritis, and panniculitis; prednisone was increased to 15 mg/day, and azathioprine was added (75 mg/day) with clinical improvement. In July 1994, the patient was readmitted because of fever, productive cough, and dyspnea of 7 weeks duration. Physical examination showed a temperature of 38.5°C, heart rate 70/min, respiratory rate 22/min, and weight 58 kg. She had bilateral respiratory rales and used her accessory respiratory muscles. Laboratory findings showed PaO_2 45 mmHg, PCO_2 21, O_2 saturation 87%; hemoglobin 11.5 g/dl, leukocytes 7100/mm^3 (lymphocytes 2.7%, neutrophils 96.4%), and an interstitial infiltrate on chest X-ray (Fig. 1).

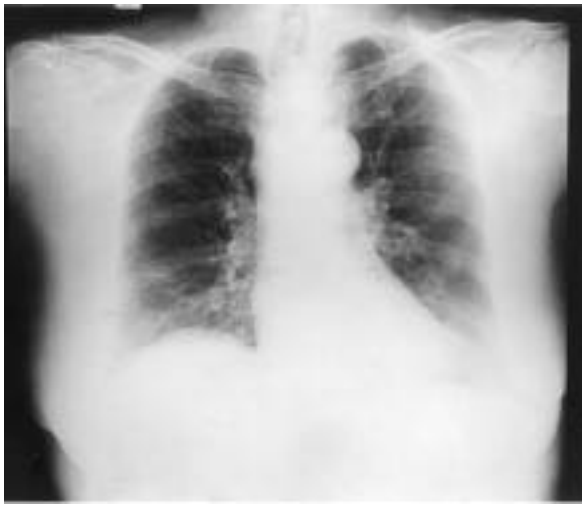
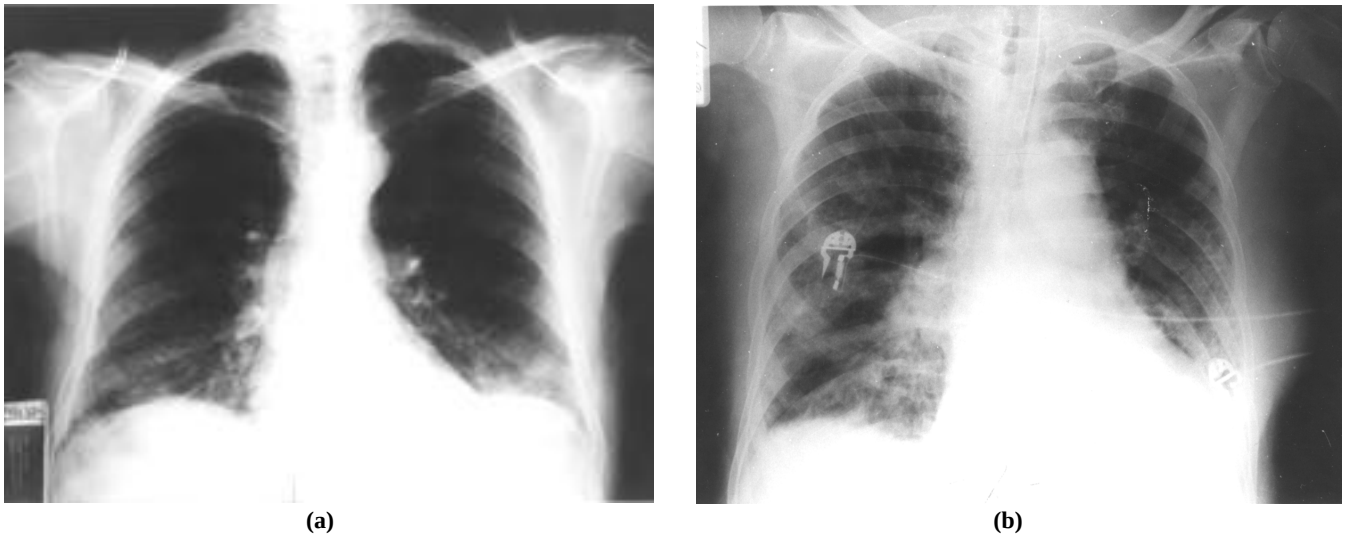


Fig. 1. Chest X-ray of a female patient with SLE and secondary antiphospholipid syndrome of long duration (Case 1), who developed tuberculosis.

The patient was treated with supplementary oxygen, erythromycin, cotrimoxazole, and hydrocortisone (100 mg i.v. every 8 hrs). A bronchioalveolar lavage showed a positive Ziehl-Neelsen stain. Rifampicin, isoniazid, pirazinamide and ethambutol were added two days after her admission. She died due to progressive respiratory failure five days later. A susceptibility test was carried out and no resistance was shown.

Case 2

A 50-year-old male, a farmer by profession, presented to us with a 6-month history of proximal muscle weakness, weight loss and hyporexia, and fever and diaphoresis that had begun one month earlier. Physical examination showed a temperature of 37.5°C, heart rate 78/min, respiratory rate 24/min, weight 62.3 kg. He had proximal muscle weakness and hepatomegaly. Other findings included CK 5100 U/dl, and extensive inflammatory infiltrates on a muscle biopsy. A chest x-ray was normal (Fig. 2a).
Polymyositis was diagnosed, a malig-



(a) **(b)**

Fig. 2. Case 2, a male patient being treated with prednisone for polymyositis, who subsequently developed tuberculosis: (a) first chest x-ray; (b) second chest x-ray, taken one month later.

nancy was ruled out, and the patient was started on prednisone (1 mg/kg/day). He improved and was released from the hospital. One month later, he was re-admitted because of fever, dyspnea, cough, hemoptysis, and respiratory failure. Laboratory tests showed hypoxemia (PaO_2 25.7 mmHg, PCO_2 21.6 mmHg, O_2 saturation 44.6%); hemoglobin 10.1 g/dl, hematocrit 28.9%, and a white blood cell count of 8100/mm^3 (lymphocytes 20%, neutrophils 73.5%). A chest X-ray showed extensive interstitial infiltrates (Fig. 2b).

The patient required mechanical ventilation, and was started on erythromycin and cotrimoxazole. Three days later, a bronchoscopic lung biopsy was performed which showed casseous necrosis. Rifampicin, isoniazid, pirazinamide and ethambutol were administered. Four weeks later, cultures were positive for *M. tuberculosis*. He received anti-tuberculosis treatment for one year. Prednisone was tapered over a period of 4 months. The patient's polymyositis relapsed and was treated successfully with prednisone (0.5 mg/Kg) in 1996. His last visit was in February of 1998 and he has remained asymptomatic.

Case 3

A 45-year-old female was admitted because of RA in 1984. She received D-penicillamine and NSAIDs with a poor response for 2 years; her treatment was changed to low-dose steroids (prednisone 7.5 mg/day), methotrexate 10 mg/week, and sulindac 400 mg/day. In September of 1992, she was seen at the emergency room because of an abscess located in the left leg. The abscess was drained (300 ml of purulent material), and dicloxacillin (500 mg PO, tid) plus rifampicin (300 mg PO, bid) were administered.

Three weeks later, the abscess relapsed. The patient was hospitalized, and surgical drainage was required. Cultures were positive for *Staphylococcus aureus*, and cephalotine (1g i.v./6 hrs) was administered for 14 days. The patient was discharged after improvement, but the abscess was still draining. Late cultures of the abscess grew *M. tuberculosis* after 12 weeks, and treatment with isoniazid, rifampicin, ethambutol and pirazinamide was introduced for 2 months, followed by isoniazid and rifampicin for 10 more months. A good response was seen, with resolution of the abscess. When the patient was seen in September 1998 she was asymptomatic.

Results

Thirty-three patients with a systemic rheumatic disease and tuberculosis were individuated from patient records for the period 1987 - 1994. Three patients were excluded because tuberculosis was confirmed prior to the systemic rheumatic disease: one with RA, one with primary antiphospholipid syndrome, and a woman with SLE and post-transfusional HIV infection. The demographic characteristics and clinical data of the patients studied are given in Table I. The diagnoses of the systemic rheumatic diseases were: SLE in 13 patients (43.3%), RA in 7 (23%), polymyositis or dermatomyositis in 5 (16%), MCTD in 2 (6%), and one patient each with Wegener's granulomatosis, Henoch-Schönlein purpura and gout. In 23 patients (76%) the systemic rheumatic disease was clinically active at the time of the diagnosis of tuberculosis, and 16 (53%) developed tuberculosis within one year after the diagnosis of their systemic rheumatic disease. In addition, 17 patients showed a weight deficit, 4 non-insulin dependent diabetes mellitus, 3 chronic alcoholism, and 3 more chronic renal failure secondary to SLE nephritis.

The use of immunosuppressive agents in these patients is summarized in Table II; 24 patients were treated with corticosteroids, immunosuppressants or other drugs before the tuberculosis was diagnosed. Twenty-two patients received prednisone in doses between 5 to 75 mg per day for < 1 to 240 months at any time prior to their tuberculosis. In the six month period prior to the tuberculosis, the median daily dose of prednisone was higher, because one patient with gout was treated before his admission to this hospital with 3 daily 500 mg boluses of methylprednisolone. In addition, some patients were on several doses of chloroquine, methotrexate, azathioprine and cyclophospamide.

Ten patients had pulmonary tuberculosis and 20 had extra-pulmonary disease. This data is shown in Figure 3. Six of the seven patients with miliary tuberculosis had concomitant SLE.

The clinical manifestations most commonly observed were fever and weight loss. Sixteen patients had an abnormal chest X-ray. Four patients had a lobar infiltrate, 2 being apical and 2 basal (Table III). The PPD test was done in 18 patients and the results (mm of induration) are shown in Table III.

Eighteen patients had a positive culture, 6 with pulmonary tuberculosis, 6 miliary, 4 renal, one osteoarticular and one lymphatic. Susceptibility tests were carried

Table I. Clinical findings and demographic characteristics of 30 patients with systemic rheumatic diseases and tuberculosis.

A. Variable	Median	Limits (min - max)
Age (years)	41.5	14 - 66
Duration of rheumatic disease before TB (months)	12.5	< 1 - 372
Follow-up after TB (months)	18	< 1 - 72
White blood cells (mm^3)	7400	1737 - 20,500
Lymphocytes (mm^3)	1660	34 - 8300
Serum albumin (mg/dl)	2.85	1.4 - 5.6

B. Variable	n	%
Sex (female)	20	66
Past close contact with a proven case of tuberculosis (n = 18)	6/18	33
Weight deficit	17	57
1st degree	9	30
2nd degree	5	17
3rd degree	3	10

Table II. Drugs used in patients with systemic rheumatic diseases any moment or six months prior to tuberculosis.

Drug	Any moment		Six months prior	
	Median	Limits*	Median	Limits*
Prednisone				
N, %	n = 22, 73%		n = 17, 57%	
Dose in mg/day	20	5 - 75	15	5 - 625
Time in months	47.4	0.1 - 240	5	0.1 - 6
Chloroquine				
N, %	n = 6, 20%		n = 5, 17%	
Dose in mg/day	150	0 - 150	150	0 - 150
Time in months	15	1 - 30	4	1-6
Methotrexate				
N, %	n = 4, 13%		n = 3, 10	
Dose in mg/week	7.5	5 - 15	7.5	5 - 10
Time in weeks	68	8 - 122	18	8 - 24
Azathioprine				
N, %	n = 2, 7%		n = 2, 7%	
Dose in mg/day	100	100 - 150	100	100 - 150
Time in months	30	26 - 34	24	24 - 24
Cyclophosphamide				
N, %	n = 1, 3%		n = 1, 3%	
Daily dose in mg/day	50		125	
Time in months	18		4	
Without treatment				
N, %	n = 6, 20%		n = 8, 27%	

*Limits: minimum - maximum.

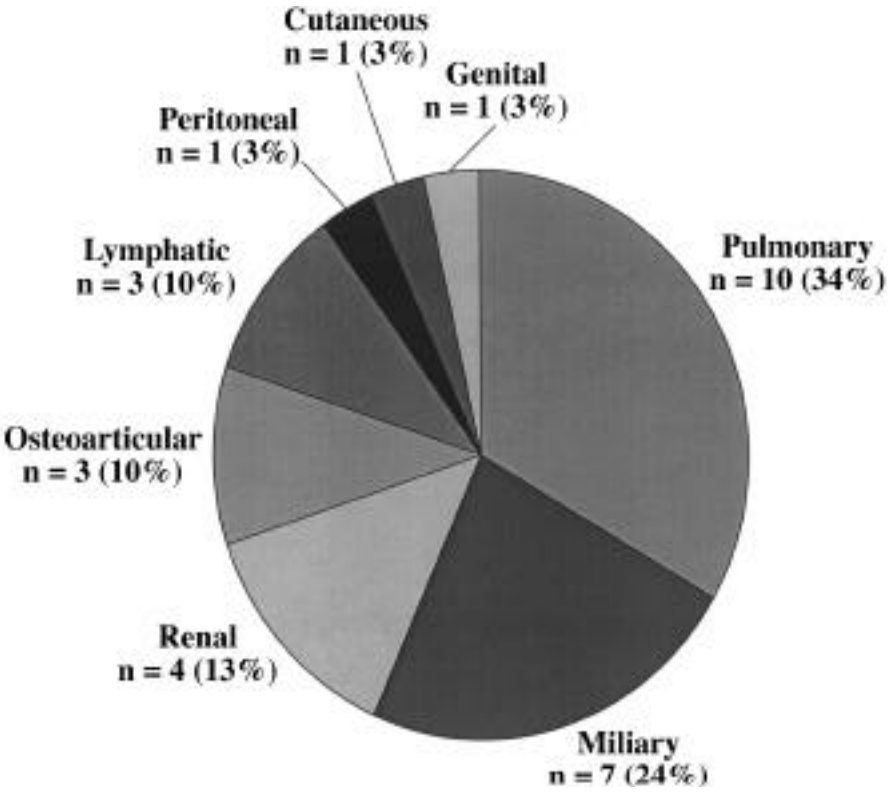


Fig. 3. Localization of tuberculosis in patients with systemic rheumatic disease.

out for 7 isolates, and only one was found to be multi-drug resistant.

All patients initially received 3 or 4 anti-tuberculosis drugs for up to 6 months, and then completed their treatment with two drugs (Table IV). Twenty-five patients (83%) responded successfully to the therapy, as is shown in Table IV. The mean interval between the initiation of the tuberculosis symptoms and the diagnosis was 44 days (range 3 - 128); and the mean time between the first consultation and administration of the antibiotics was 18.4 days (range 5 - 45).

Three patients relapsed. The first was a woman with SLE (on steroids 60 mg/day of prednisone for two months) and miliary tuberculosis, who was treated with four drugs for 4 months, then ethambutol and pirazinamide (due to isoniazid hepatitis) for 8 more months. She relapsed two years later after a new course of immunosuppressants, because of vasculitis. She received rifampicin, ethambutol, pirazinamide, ciprofloxacin and amikacin for 2 months followed by rifampicin, ethambutol and pirazinamide for 16 more months. Susceptibility testing was not done.

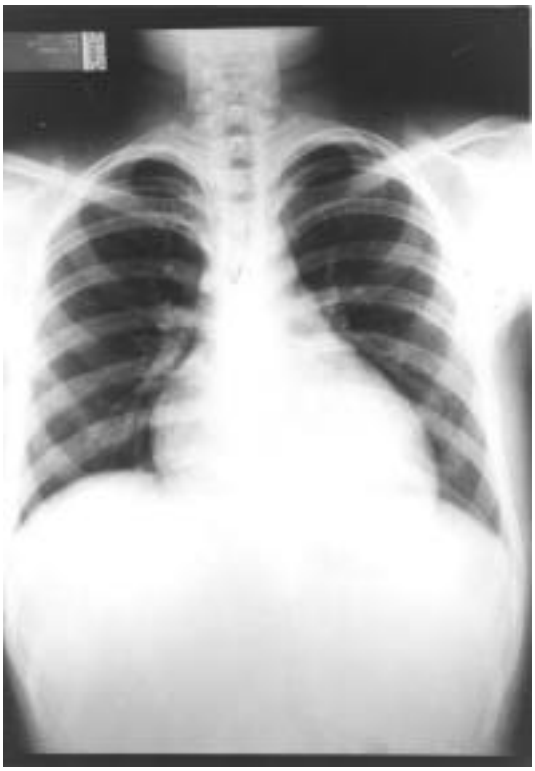
Table III. Clinical manifestations of tuberculosis in patients with systemic rheumatic disease.

	n	(%)
Clinical manifestation		
Fever	20	(67)
Weight loss	20	(67)
Diaphoresis	18	(60)
Productive cough	16	(53)
Lymph node enlargement	13	(43)
Dyspnea	10	(33)
Hemoptysis	8	(27)
Abnormal chest film	16	(53)
Micronodular infiltrate	7	
Pneumonia apical with cavitation	5	
Pneumonia lobar	4	
Pleural thickening	3	
Solitary nodule	2	
Pneumothorax	1	
PPD reaction (RT-23 2U)	18	(60)
Induraton < 10 mm	10	(56)
Induration 10 - 20 mm	6	(33)
Induration > 20 mm	2	(11)

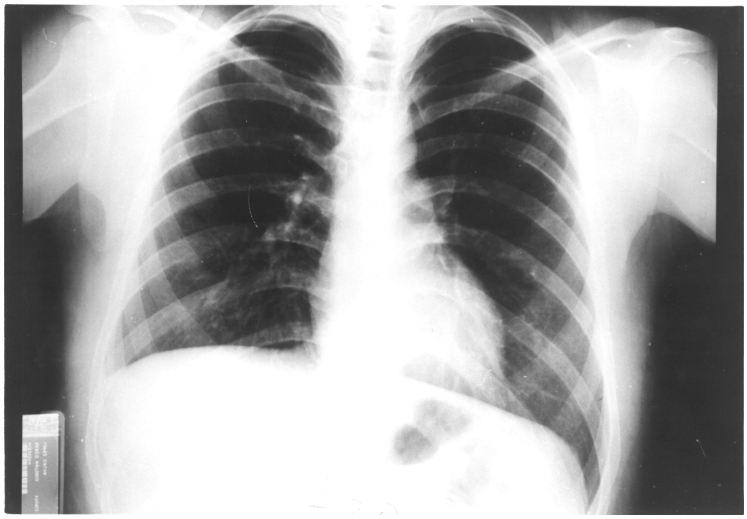
Table IV. Treatment and outcome of tuberculosis in patients with systemic rheumatic diseases.

		Initial treatment		Subsequent treatment	
No.	%	Drugs	Time	Drugs	Time
15	51	INH + EMB + RIF	2 months	INH + RIF	10 months
10	34	INH + EMB + RIF + PZA	2 months	INH + RIF	10 months
1 relapse*	3	INH + EMB + RIF + PZA	6 months	INH + RIF	6 months
1 relapse**	3	INH + EMB + RIF + PZA	4 months	ETB + PZM	8 months
1 relapse***	3	INH + EMB + RIF	6 months	None	0 months
1 death	3	INH + EMB + RIF + PZA	10 days		
1 death	3	INH + EMB + RIF + PZA	15 days		
Therapy response					
Good	25, 83				
Relapse	3, 10				
Deaths by tuberculosis	2, 7				
Hepatotoxicity	2, 7				

INH = isoniazid (dosage 10 mg/Kg/day, maximum 300 mg/day); EMB = ethambutol (800-1200 mg/day); RIF = rifampicin (300 mg/day); PZA = pirazinamide (1500 mg/day).
*, **, *** Patients with relapse (see text for description).



(a)



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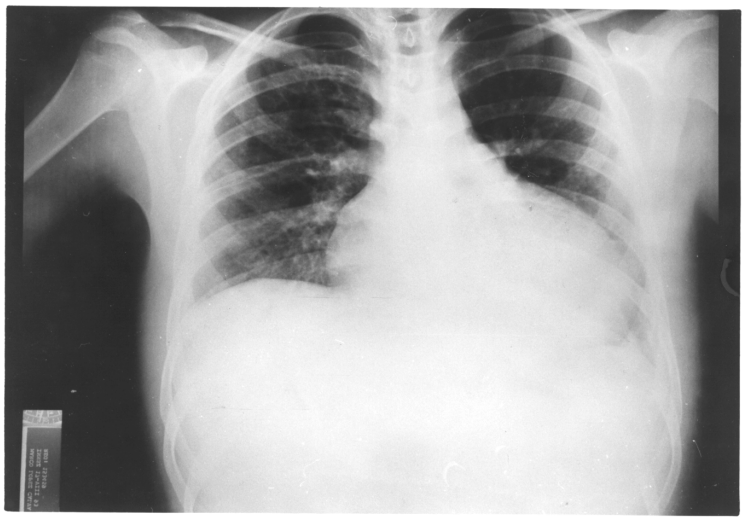

(c)

Fig. 4. Sequential chest x-rays in a male patient with SLE who developed tuberculosis while on prednisone: (**a**) tuberculosis with pulmonary cavities in upper right lobe; (**b**) 12 months later, the tuberculosis was cured; (**c**) 19 months later the patient suffered a relapse of tuberculosis.

The second was a man with PM and genital tuberculosis who was treated with isoniazid, rifampicin and ethambutol for six months and was cured. Four years later steroids were started (45 mg/day) for PM, and one month later the patient developed cutaneous tuberculosis; he was successfully treated with the same therapy. Susceptibility testing was not performed.

The third was a man with SLE who developed tuberculosis while on prednisone (30 mg/day). He was treated with a four-drug regimen for six months followed by isoniazid and rifampicin for six more months. He received 4 monthly boluses of cyclophosphamide, and prednisone (60 mg/day) because of nephritis. Three months later, he developed pulmonary multi-drug resistant tuberculosis, and was treated with streptomycin, ethambutol, pirazinamide, ciprofloxacin and amoxicillin/clavulanate for 14 months with a favorable clinical response. Figure 4 shows sequential chest X-rays for this patient.

Two patients developed hepatitis secondary to isoniazid after three weeks of therapy. A favorable response was observed once the drug was stopped. Both patients continued their anti-tuberculous treatment with rifampicin, ethambutol and pyrazinamide for 9 more months; one of them was cured, and the other was previously described.

Two women with SLE and miliary tuberculosis died of acute respiratory failure after 5 and 15 days of anti-tuberculous therapy, respectively. The period between the initial symptoms of tuberculosis and hospitalization was 46 and 78 days, respectively, and the interval to the initiation of therapy was 48 and 93 days, respectively. The autopsy revealed extensive pulmonary damage due to *M. tuberculosis* in both patients. A drug susceptibility test was carried out in one of these cases, and resistance was not observed.

Discussion

We describe here the characteristics of 30 patients with systemic rheumatic disease and tuberculosis seen at a referral center in Mexico City. The incidence of tuberculosis in Mexican patients with systemic rheumatic diseases has been estimated to be 2.5% (9). Our data shows that tuberculosis in patients with a systemic rheumatic disease demonstrates a specific pattern, i.e. a high proportion of extra-pulmonary tuberculosis, which increases the difficulty of diagnosing and treating this infection. In this regard our findings are similar to those reported by Feng *et al.* (11). Most of our patients had an active systemic rheumatic disease of less than one year's duration, and required therapy with corticosteroids or other immunosuppressants in the six months prior to the diagnosis of tuberculosis. There was a association between miliary tuberculosis and SLE. Tuberculosis was diagnosed based on the clinical data in all but one case.

Mortality due to tuberculosis was low in this study, and was comparable to that observed in non-immunocompromised patients (24). This may be explained by the higher rate of clinical suspicion, the short interval between diagnosis and therapy, and perhaps also by a lesser severity or activity of the rheumatic disease. In patients with SLE and miliary tuberculosis the mortality rate was high; these patients had in common a delay in the diagnosis of tuberculosis and the initiation of therapy, an aggressive rheumatic disease, and the use of high doses of corticosteroids. The rate of tuberculosis relapse was 10% in spite of appropriate therapy; once again, these patients showed a weight deficit, intense rheumatic activity, and required aggressive immunosuppressant therapy. However, our sample size is small.

Hepatotoxicity caused by anti-tuberculous therapy was three-fold greater than that observed in the general population, in spite of the relatively young age of the patients. This could be explained by a co-morbidity factor, and multiple drug use which is known to increase the risk of toxicity (25). Regarding prophylaxis with isoniazid, most of our patients either did not receive any prophylaxis or else received an inadequate dosage. Most of our patients had a PPD response of 5 mm or more of induration, but less than half of them developed > 10 mm induration. The prevalence of a positive PPD response (> 10 mm of induration) ranges from 54% and 96% in tuberculous patients without co-morbidity (26). Patients with extra-pulmonary tuberculosis, especially those with the miliary forms, and those with co-morbidity show a lesser response (27); in the Mexican population this can range from 43% to 75% (28). These findings may suggest that a PPD response of > 10 mm of induration in patients with systemic rheumatic diseases correlates highly with active tuberculosis, but lesser responses (< 10 mm of induration) do not rule out the disease. A larger sample size and prospective studies will be required to evaluate correctly the points regarding hepatotoxicity, prophylaxis with isoniazid, and the PPD test in patients with systemic rheumatic diseases.

There were some problems relating to the design of this study which merit discussion. For example, patients with negative cultures would not have been diagnosed and therefore would not have been included in our study, thus causing an underestimation bias. It was also difficult to evaluate compliance to the tuberculosis treatment, a point which may be of particular relevance in those patients with relapse. The patients who died were all in-patients who were on anti-tuberculous treatment administered in the hospital by nasogastric tube. We believe that their treatment was too short; probably the drugs were not fully absorbed, or they had a very high bacillary load, which could have had an impact on their outcome. Drug susceptibility was evaluated in 7 of 18 isolates and only in one case of relapse, which showed multi-drug resistant isolates. For this reason susceptibility could not be evaluated in this study as a prognosis factor. In the same way, re-infection and re-activation could not be excluded by RLFP.

Weight deficit was evaluated instead of malnutrition, primarily because of the retrospective nature of our study. Those patients with a weight deficit were also suffering from hypoalbuminemia, anemia, lymphopenia and, possibly, malnutrition. It is difficult to know whether the weight deficit was a consequence of the infection, the systemic rheumatic disease, the co-morbidity or other factors (low food intake).

Nevertheless, we believe that our results provide some important indications for the clinical management of patients with

tuberculosis and systemic rheumatic diseases, especially in countries with high rates of tuberculosis, such as Mexico. Our findings suggest that in such patients the presence of fever, weight loss, cough and an abnormal chest x-ray should lead the clinician to check for the presence tuberculosis, especially in those who are on steroids or immunosuppressants. In these patients, tuberculosis has a distinct behavior with a high proportion of extra-pulmonary disease, and if tuberculosis is suspected, treatment should be started as soon as possible.

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