Tuberculosis in a cohort of patients with systemic lupus erythematosus

Rocío González León, Rocío Garrido Rasco, Eduardo Chinchilla Palomares, Francisco José García Hernández, M. Jesús Castillo Palma, and Julio Sánchez Román*

Unidad de Colagenosis e Hipertensión Pulmonar, Servicio de Medicina Interna, Hospital Universitario Virgen del Rocío, Sevilla, Spain

ARTICLE INFO

ABSTRACT

Objectives: 1) To study tuberculosis (TB) infection in a cohort of patients with systemic lupus erythematosus (SLE) and to compare its frequency and characteristics with that of others series. 2) To look for differential characteristic among SLE patients with and without TB. 3) To investigate if there was any relationship between TB's most severe forms and higher doses of glucocorticoids (GC) or other immunosuppressants.

Patients and method: Retrospective review of medical records of 789 SLE patients and description of the clinical characteristics of 13 cases of active TB infection among them. Bibliographical search in MEDLINE-PubMed of the SLE/TB series published, using the terms: infection, tuberculosis, systemic lupus erythematosus. Comparative study of clinical, biological and therapeutic differences between cases (SLE/TB+) and controls (SLE/TB) using \( \chi^2 \) and Fisher exact test.

Results: Thirty patients with active tuberculosis were detected (10 women, average age 36 years/SD 11.2/ prevalence 1.6%). Nine (69.2%) of them were primary infections and 4 (30.8%) reactivations. Microbiological diagnosis (smear examination for acid-fast bacilli and/or culture on Lowestein-Jensen medium) was established in 11 patients (84.6%). TB Pulmonary manifestations was present in 9 patients (69.2%) and extrapulmonary manifestations were found in 8 (61.5%); 6 of them (46%) were disseminated forms. Nine (69.2%) patients were on GC therapy at the moment TB was diagnosed. Four of the TB patients died (30.8%). Myositis was more frequent in TB cases (P<.05). This data is similar to that reported in the literature.

Conclusions: In our series, TB mortality was high (30.8%) in a patients with SLE. Frequency of extrapulmonary forms was double than that described in the Spanish population. Patients with higher GC dose had more severe forms of TB.

© 2009 Elsevier España, S.L. All rights reserved.

Tuberculosis en una cohorte de pacientes con lupus eritematoso sistémico

RESUMEN

Objetivos: Analizar los casos de tuberculosis (TB) en una cohorte de pacientes con lupus eritematoso sistémico (LES) y comparar la frecuencia y características de la TB en nuestra serie con las de otras series publicadas; identificar características diferenciales entre los pacientes que presentaron TB y los que no la presentaron, y evaluar si las formas más graves se relacionaron con dosis más altas de glucocorticoides (GC) u otros inmunosupresores.

Material y método: Análisis descriptivo de 13 pacientes con TB de una serie de 789 pacientes con LES. Revisión de las historias clínicas de los casos. Búsqueda bibliográfica en MEDLINE-PubMed de las series LES/TB publicadas, utilizando los términos «infección», «tuberculosis», «lupus eritematosus». Estudio comparativo de casos (LES/TB+) y controles (LES/TB-) en cuanto a las características clínicas, de laboratorio y el tratamiento realizado, mediante test \( \chi^2 \) y test exacto de Fisher.

Resultados: Trece pacientes estuvieron afectados por TB (10 mujeres, con edad media de 36 años; DE de 11,2, y prevalencia del 1,6%). Se diagnosticaron 9 primoinfecciones (69,2%) y 4 reactivaciones (30,8%). El diagnóstico se confirmó mediante aislamiento microbiológico (baciloscopia y/o cultivo) en 11 casos (84,6%).

* Corresponding author. 
E-mail address: sanchezroman@telefonica.net, julio.sanchez.sspa@juntadeandalucia.es (J. Sánchez Román).
La TB en nuestra serie supuso una alta mortalidad (30,8%) en los enfermos con LES. Las formas extrapulmonares representaron el doble con respecto a la observada en la población general. Los pacientes que recibieron dosis mayores de GC fueron los que presentaron formas más graves de TB. Los datos son similares a los publicados en la mayoría de las series nacionales y extranjeras.

© 2009 Elsevier España, S.L. Todos los derechos reservados.
Table 1
Comparison of clinical characteristics

<table>
<thead>
<tr>
<th>Clinical manifestations</th>
<th>SLE/TB+ (n=13), n (%)</th>
<th>SLE/TB− (n=776), n (%)</th>
<th>P</th>
<th>95% CI/OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Photosensitivity</td>
<td>5 (38.5)</td>
<td>339 (43.7)</td>
<td>NS</td>
<td>0.26-2.48/0.81</td>
</tr>
<tr>
<td>Erythema nodosum/panniculitis</td>
<td>2 (15.4)</td>
<td>23 (2.9)</td>
<td>.061*</td>
<td>1.25-38.29/5.95</td>
</tr>
<tr>
<td>Malar erythema</td>
<td>6 (46.1)</td>
<td>480 (61.8)</td>
<td>NS</td>
<td>0.18-1.59/0.53</td>
</tr>
<tr>
<td>Discoid lupus</td>
<td>3 (23.1)</td>
<td>173 (22.3)</td>
<td>NS</td>
<td>0.28-3.84/1.04</td>
</tr>
<tr>
<td>Mucosal affection</td>
<td>5 (38.5)</td>
<td>293 (37.7)</td>
<td>NS</td>
<td>0.33-3.18/1.03</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>6 (46.1)</td>
<td>201 (25.9)</td>
<td>NS</td>
<td>0.81-7.38/2.45</td>
</tr>
<tr>
<td>Arthralgia/arthritis</td>
<td>12 (92.3)</td>
<td>636 (81.9)</td>
<td>NS</td>
<td>0.34-20.48/2.64</td>
</tr>
<tr>
<td>Myositis</td>
<td>4 (30.8)</td>
<td>75 (9.6)</td>
<td>.046</td>
<td>1.25-11.81/4.15</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>4 (30.8)</td>
<td>126 (16.2)</td>
<td>NS</td>
<td>0.69-7.56/2.29</td>
</tr>
<tr>
<td>Lung involvement</td>
<td>4 (30.8)</td>
<td>218 (28.1)</td>
<td>NS</td>
<td>0.35-3.73/1.14</td>
</tr>
<tr>
<td>Renal involvement</td>
<td>6 (46.1)</td>
<td>275 (35.4)</td>
<td>NS</td>
<td>0.52-4.69/1.56</td>
</tr>
<tr>
<td>Neurological involvement</td>
<td>3 (23.1)</td>
<td>245 (31.6)</td>
<td>NS</td>
<td>0.18-2.38/0.65</td>
</tr>
<tr>
<td>Sjögren’s syndrome</td>
<td>5 (38.5)</td>
<td>229 (29.5)</td>
<td>NS</td>
<td>0.48-4.61/1.49</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; NS, not significant; OR, odds ratio; SLE, systemic lupus erythematosus; TB, tuberculosis.

*Fisher exact test.

Table 2
Laboratory characteristics

<table>
<thead>
<tr>
<th>Laboratory findings</th>
<th>SLE/TB+ (n=13), n (%)*</th>
<th>SLE/TB− (n=776), n (%)*</th>
<th>P</th>
<th>95% CI/OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td>8 (61.5)</td>
<td>411 (52.9)</td>
<td>NS</td>
<td>0.46-4.38/1.42</td>
</tr>
<tr>
<td>Haemolytic anaemia</td>
<td>3 (23.1)</td>
<td>69 (8.9)</td>
<td>NS</td>
<td>0.83-11.4/3.07</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>9 (69.2)</td>
<td>420 (54.1)</td>
<td>NS</td>
<td>0.58-6.24/1.91</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>13 (100)</td>
<td>618 (79.6)</td>
<td>NS</td>
<td>0.41-116.96/6.92</td>
</tr>
<tr>
<td>Thrombocytopoenia</td>
<td>2 (15.4)</td>
<td>188 (24.2)</td>
<td>NS</td>
<td>0.12-2.59/0.57</td>
</tr>
<tr>
<td>CRP&gt;5 mg/l</td>
<td>8 (61.5)</td>
<td>322 (42.8)</td>
<td>NS</td>
<td>0.69-6.59/2.14</td>
</tr>
<tr>
<td>Syphilis serology</td>
<td>0 (0)</td>
<td>58.75)</td>
<td>NS</td>
<td>0.003-775/0.45</td>
</tr>
<tr>
<td>ANA+ (1/80)</td>
<td>13 (100)</td>
<td>716 (92.3)</td>
<td>NS</td>
<td>0.13-38.81/2.28</td>
</tr>
<tr>
<td>Pattern**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffuse</td>
<td>1 (7.7)</td>
<td>1 (7.7)</td>
<td>NS</td>
<td>3.29-1.97/0.25</td>
</tr>
<tr>
<td>Mottled</td>
<td>6 (46.1)</td>
<td>8 (61.5)</td>
<td>NS</td>
<td>0.29-2.65/0.88</td>
</tr>
<tr>
<td>Mixed</td>
<td>5 (38.5)</td>
<td>3 (23.1)</td>
<td>NS</td>
<td>0.21-2.61/0.65</td>
</tr>
<tr>
<td>Nuclear</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NS</td>
<td>2.40-6.96/0.41</td>
</tr>
<tr>
<td>Anti-native DNA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ENA</td>
<td>6 (46.1)</td>
<td>277 (35.7)</td>
<td>NS</td>
<td>0.51-4.64/1.54</td>
</tr>
<tr>
<td>SSA</td>
<td>3 (23.1)</td>
<td>192 (24.7)</td>
<td>NS</td>
<td>0.25-3.35/0.91</td>
</tr>
<tr>
<td>SSB</td>
<td>1 (7.7)</td>
<td>78 (10.1)</td>
<td>NS</td>
<td>9.57-58.1/0.75</td>
</tr>
<tr>
<td>RNP</td>
<td>1 (7.7)</td>
<td>112 (14.4)</td>
<td>NS</td>
<td>0.004-3.83/0.49</td>
</tr>
<tr>
<td>Sm</td>
<td>2 (15.4)</td>
<td>39 (5)</td>
<td>NS</td>
<td>0.74-16.03/3.44</td>
</tr>
<tr>
<td>Anticentromere</td>
<td>1 (7.7)</td>
<td>9 (1.16)</td>
<td>NS</td>
<td>0.83-60.53/7.10</td>
</tr>
<tr>
<td>Anticardiolipin</td>
<td>3 (23.1)</td>
<td>304 (39.2)</td>
<td>NS</td>
<td>0.13-1.71/0.47</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; CRP, C reactive protein; DNA, deoxyribonucleic acid; NS, not significant; OR, odds ratio; SLE, systemic lupus erythematosus; TB, tuberculosis.

*Percentages refer to the total of each group.
**Triple substrate/Hep2 substrate.

Table 3
Immunosuppressive and immunomodulatory treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SLE/TB+ (n=13), n (%)</th>
<th>SLE/TB− (n=776), n (%)</th>
<th>P</th>
<th>95% CI/OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>GC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low doses (&lt;30 mg/day)*</td>
<td>1 (7.7)</td>
<td>83 (10.7)</td>
<td>NS</td>
<td>0.09-5.41/0.69</td>
</tr>
<tr>
<td>High doses (&gt;30 mg/ day)**</td>
<td>9 (69.2)</td>
<td>466 (60.0)</td>
<td>NS</td>
<td>0.46-4.90/1.49</td>
</tr>
<tr>
<td>Cyclophosphamide (boluses)</td>
<td>5 (38.5)</td>
<td>138 (22.9)</td>
<td>NS</td>
<td>0.52-4.94/1.59</td>
</tr>
<tr>
<td>Antimalarials</td>
<td>8 (61.5)</td>
<td>508 (65.5)</td>
<td>NS</td>
<td>0.27-2.60/0.84</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>11 (84.6)</td>
<td>577 (74.3)</td>
<td>NS</td>
<td>0.42-8.03/1.89</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>3 (23.1)</td>
<td>221 (28.5)</td>
<td>NS</td>
<td>0.21-2.76/0.75</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>2 (15.4)</td>
<td>130 (16.7)</td>
<td>NS</td>
<td>0.20-4.12/0.90</td>
</tr>
<tr>
<td>Immunglobulins</td>
<td>4 (30.8)</td>
<td>93 (11.9)</td>
<td>NS</td>
<td>0.98-10.80/3.26</td>
</tr>
<tr>
<td>Rituximab</td>
<td>1 (7.7)</td>
<td>54 (6.9)</td>
<td>NS</td>
<td>0.14-8.73/1.11</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>1 (7.7)</td>
<td>63 (8.1)</td>
<td>NS</td>
<td>0.12-7.37/0.94</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; GC, glucocorticoids; NS, not significant; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio; SLE, systemic lupus erythematosus; TB, tuberculosis.

*Patients who only took low doses.
**High doses of corticosteroids also include low doses received at other moments.
The diagnosis was confirmed by microbiological isolation (smear tests and/or mycobacterial culture) in 11 cases (84.6%); smear test was positive in 10 of them and isolation through culture in 5. For 2 other patients, it was not possible to obtain a microbiological diagnosis, although the combination of different data (epidemiological, clinical, radiological and anatomopathological) and the response to tuberculostatic therapy supported the diagnosis at the time. Specifically, these were patients B and D. Patient B presented only lymph node involvement with anatomopathological findings in biopsy suggestive of TB aetiology (caseating granulomatous lymphadenitis) and had a significant family history (a sister with lymph node TB). Patient D presented bone TB (spondylodiscitis) and subsequently pleuropulmonary TB; all in the context of silicotuberculosis. Both patients responded to anti-TB treatment, which further supported the diagnosis, in the context of the above facts. The result of the tuberculin test by Mantoux skin test was available for 10 patients; in 8 of these, it was positive (induration >10mm) and in the remaining 2 it was negative.

Nine patients (69.2%) presented pulmonary involvement (including the cases with pulmonary involvement in the context of disseminated forms): 5 cases with unilateral involvement (55.5%) and 4 with bilateral involvement (44.4%), and 2 cases with mediastinal node involvement (diagnosed with silicotuberculosis). The chest radiography pattern was consolidative in 4 patients (44.4%), miliary in 2 patients (22.2%), and nodular in 2 patients (22.2%). Cavitaton was observed in 3 cases (33.3%) and pleural involvement in another 3 (33.3%). Eight patients (61.5%) presented extrapulmonary forms, there were 5 (38.5%) with a ganglion form, 3 (23.1%) with a bone form, 2 (15.4%) with a muscular form, 1 (7.7%) with a cutaneous form and another with central nervous system involvement. Of the 8 extrapulmonary forms, 6 (46.2%) were disseminated. The disease was multidrug-resistant (as well as multivisceral) in 1 case: iliospools and subpectoral muscle abscesses and involvement of peripheral lymph nodes, bone (spondylodiscitis) and lung.

At the time of TB diagnosis, 9 patients (69.2%) were being treated with GC; in 6 as a single immunosuppressant treatment, in 2 associated to cyclophosphamide boluses and in 1 associated to cyclophosphamide and rituximab. The most severe forms were observed in patients with higher cumulative GC doses (Patients A, C, E, G, I).

The determination of the CRP at the time of TB diagnosis was available for 9 patients and was increased in 8 patients (88.8%). Three of them presented signs of SLE activity (skin, joint, renal and general forms) and in the remaining 5, the immunopathological process was inactive.

Correct tuberculostatic treatment could be completed successfully in 9 patients (6 months for pulmonary forms and 9-12 months for extrapulmonary/disseminated forms). One of these patients suffered liver toxicity from pyrazinamide (resolved by withdrawing the drug and replacing it with streptomycin) and another suffered isoniazid toxicity after 2 months of treatment (skin rash and hypertransaminasemia), with good response after withdrawing it and substituting ethambutol. The treatment was completed successfully in both cases. In 4 patients, it was not possible to complete the treatment due to death during its course: 3 patients (Patients E, G, I) suffered sepsis (miliary in 2 cases and with inconclusive results in the autopsy of the third) with multiple organ failure after 2 weeks of tuberculostatic treatment in 2 cases and after 7 weeks in another. Patients E and G presented SLE without severe visceral impact and only Patient G received GC treatment at high doses; Patient I presented SLE with severe visceral involvement (lupus nephritis) and received treatment with GC and cyclophosphamide boluses when TB was diagnosed. None presented associated comorbidity apart from SLE and age did not exceed 55 years in any of them. The fourth patient suffered bronchogenic tuberculosis dissemination and hepatotoxicity from rifampicin in the 5th week of treatment, which forced the withdrawal of TB drugs for 7 days; treatment was subsequently restarted with isoniazid, pyrazinamide, ethambutol and streptomycin, but could only be maintained for 15 days due to death. The patient had been diagnosed with SLE 6 years before TB; she had presented cutaneous, pulmonary, cardiac and joint involvement, and at the time of TB diagnosis was being treated with GC and cyclophosphamide for lupus activity. The average cumulative GC dose in the 4 patients who died was 11,437.5 mg (SD: 329.8); in the 9 patients who survived, it was 9,576.7 mg (SD: 19,209.2) with no significant differences (variance=5.32; P=0.167; Student t=18; P=0.8584).

A total of 50% of the deceased were receiving cyclophosphamide at the time of TB diagnosis, compared to 33.3% of those who survived (P=0.05; 95% CI: 0.18 to 22.01; OR: 2). The 4 patients who presented reactivation after SLE diagnosis evolved favourably.

Mortality was 30.8%. All cases with fatal outcome were diagnosed with TB prior to death.

**Discussion**

The prevalence of TB in our series was lower than in other published series (Table 5), higher than in the general population and comparable with that of another Spanish group, although somewhat lower (1.3%) than in another Spanish series published recently.
Variations in the TB prevalence observed in different studies were parallel to the TB prevalence in the global population in each of the countries considered (Table 5). Balakrishnan et al.\(^{10}\) reported a somewhat higher frequency of pulmonary involvement (82.3\%) than we observed, as well as a higher prevalence of the miliary pattern (35\%). In the series of Navarra et al.\(^6\) this pattern was observed in a similar proportion to ours (18.5\%). Other authors report a frequency for the extrapulmonary form very similar to that observed by us\(^{10-11}\) and almost double that in the general population, taking into account that in the latter case the extrapulmonary disease may be present in one third of the cases (33.3\%). In contrast, the extrapulmonary form was lower in the series of Navarra et al.\(^6\) and Balakrishnan et al.\(^{12}\) (Table 6). As for the Spanish studies, the group of Vadillo\(^9\) reports 3 cases of TB and only 1 with extrapulmonary involvement (33.3\%), while the group of Erdozain\(^{10}\) reports another 3 cases but none with this kind of involvement.

Concerning the role of immunosuppressants as inducers of development of infections, Prior et al.\(^{12}\) analysed a group of 100 patients with SLE who had received cyclophosphamide and high GC doses and identified the infections suffered during treatment and for 3 months afterwards. They observed a statistically higher frequency in patients who were concomitantly treated with GC and cyclophosphamide than in patients treated only with high doses of GC. Other studies offered similar findings.\(^{9,19,10}\)

The mortality due to TB observed in our group represents a value up to 90 times higher than in the general population if we take into account that the rate of TB mortality in Spain in 2002 was 4/100,000 inhabitants.\(^{18,19}\) This figure is comparable with that of other series but is in contrast with reports by Erdozain et al.\(^{10}\) Its three cases evolve favourably and with no complications despite being pharmacologically immunosuppressed (prednisone+azathioprine/cyclophosphamide). None carried out prophylaxis with isoniazid. One limitation of our study is its retrospective nature and the extensive period of time considered. However, 3 of the 4 patients who presented a fulminant course of TB were diagnosed between 2001 and 2009. Consequently, we can take homogeneity in the management of both TB and SLE for granted; therefore, our mortality data can be compared with the series of Erdozain et al. (study period considered: 1994-2003).

More frequent renal involvement has been reported in patients with SLE and TB, and lupus nephritis is therefore considered as a risk factor for TB.\(^{20-22}\) Up to 46.1\% of our patients with TB presented renal involvement, but with no statistically significant difference compared to the SLE/TB- group. Statistically significant differences were found for only muscular involvement; significance was almost reached for erythema nodosum/panniculitis (both manifestations being more frequent in the SLE/TB+ group).

For years, there have been attempts to relate CRP elevation with the development of infection rather than with disease activity in SLE patients. Borg et al.\(^{21}\) published a prospective study of 2 years duration in 1990 that analysed CRP elevation in 71 patients with SLE. They noted that, in the absence of serositis, CRP determination is useful for differentiating infectious disease from lupus activity, so a CRP value greater than 60 mg/l, in the absence of serositis, should suggest an infectious cause. The CRP elevation observed during outbreaks of activity was lower than this value. Very similar results had already been reported by Becker et al.\(^{22}\) in 1980. In contrast to the above, authors such as Morrow\(^22\) did not find such a difference when studying patients with SLE and TB. The number of cases registered in our series was too small to draw conclusions in this regard.

Several authors have proposed treating latent tuberculosis infection with isoniazid in all patients with SLE\(^9,14,20-22\); however, the effectiveness of this practice is not well established. Published data are scarce and of low weight.\(^{23,24}\) In short, it has been suggested that an isoniazid dose of 300 mg/day for 6 months could be useful in preventing TB infection in countries with a high TB prevalence, regardless of tuberculin test results. However, the usefulness of the tuberculin test and chest radiograph is not yet well established in the population of patients with systemic autoimmune disease and treatment with prednisone at doses higher than 15 mg/day for over 3 months.\(^{25}\) The reason for this is because this usefulness can vary depending on geographical areas and further studies are therefore required to determine what tests should be used in TB screening, under what circumstances prophylaxis is necessary and what type of prophylaxis is the most adequate.\(^{26}\) Consequently, in these patients the decision to treat latent tuberculosis infection must be individualised, after a careful evaluation of the benefits and risks. It is in this aspect that the greatest discrepancies exist between American and European literature, as the latter excludes them from its recommendations.\(^{20}\) In our unit, the performance of the tuberculin test is included in the initial study protocol for all patients with suspected SLE; however, treatment of a latent tuberculosis infection with isoniazid is not carried out systematically (only 1 of our patients with SLE and TB had followed it). Therefore, we cannot provide any clarifying information regarding the usefulness of treatment for latent tuberculosis infection with isoniazid in patients with SLE who are to receive GC.

In summary, the prevalence of TB in our population of patients with SLE (789) was 1.6\% and it presented a high mortality (30.8\%). The organ most affected was the lung (69.2\%). Extrapulmonary tuberculosis accounted for 61.5\% of our cases, practically twice that in the general population. We did not find an increase in the frequency of renal involvement in patients with TB nor did we find statistically significant differences in the immunosuppressive treatment received by both groups. Although patients who received higher doses of GC were also the ones with more severe forms of TB, the difference was not statistically significant. The elevation of CRP values could be used as a marker of infection rather than of inflammatory activity in these patients, although further studies are needed to support this claim.

**Conflict of interests**

The authors declare no conflict of interests.
Acknowledgements

The authors wish to thank Dr. D. Adolfo Baloira Villar for his kind assistance in reviewing this work.

References