Predicting adverse outcomes in primary Sjögren’s syndrome: identification of prognostic factors

P. Brito-Zerón, M. Ramos-Casals, A. Bove, J. Sentis and J. Font

Objective. To identify features present at diagnosis that were prospectively associated with adverse outcomes in a large cohort of patients with primary Sjögren’s syndrome (SS).

Methods. Two hundred and sixty-six patients diagnosed with primary SS in our department between 1984 and 2002 were consecutively included and followed up. Outcomes measured were vasculitis, B-cell lymphoma and death. Cox regression analysis was used to evaluate the effect of variables at diagnosis on outcomes.

Results. Twenty-five (9%) patients developed vasculitis. Multivariate analysis identified parotid scintigraphy grades III or IV (HR 3.55, \( P < 0.05 \)) and C4 levels <0.82 g/l (HR 7.54, \( P = 0.016 \)) as predictive factors of lymphoma development. Twenty-five (9%) patients died during follow-up. Systemic involvement (HR 4.51, \( P = 0.022 \)), vasculitis (HR 4.58, \( P = 0.042 \)), C4 levels <0.11 g/l (HR 5.47, \( P = 0.027 \)) and cryoglobulins (HR 4.58, \( P = 0.013 \)) were independently associated with death. The presence of at least two of the above-mentioned predictive factors (parotid scintigraphy, vasculitis, hypocomplementaemia and cryoglobulinaemia) was associated with a lower survival in comparison with patients with no factor (log rank and Breslow tests <0.001).

Conclusion. The main prognostic factors for an adverse outcome identified in our cohort of patients with primary SS were vasculitis, severe involvement in parotid scintigraphy, hypocomplementaemia and/or cryoglobulins at diagnosis. Patients with at least two of these factors need a closer follow-up.

Key words: Sjögren syndrome, Mortality, Vasculitis, Hypocomplementaemia, Cryoglobulins.

Introduction

Sjögren syndrome (SS) is a systemic autoimmune disease that presents with sicca symptomatology of the main mucous surfaces [1]. The histological hallmark is a focal lymphocytic infiltration of the exocrine glands, determined by a biopsy of the minor labial salivary glands [2]. The spectrum of the disease extends from sicca syndrome to systemic involvement [3, 4]. Few studies have prospectively analysed the outcome of patients with primary SS, a disease characterized by a chronic, insidious evolution [5–9]. However, some patients with primary SS may present a complicated evolution of the disease due to the development of vasculitic involvement and the high incidence of lymphoma, which are closely related to a higher risk of death [10, 11]. The identification of markers prospectively associated with a poor prognosis [6, 12] could play a significant role in identifying those patients requiring a closer follow-up.

The aim of this study was to identify those features present at diagnosis that were prospectively associated with adverse outcomes (development of vasculitis, lymphoma or death) in a large cohort of Spanish patients with primary SS.

Patients and methods

Study cohort and observation time

The study cohort included all patients diagnosed with primary SS by our Department of Autoimmune Diseases between 1984 and 2002 according to the 1993 European criteria [13]. Since a new set of classification criteria appeared in 2002, a retrospective re-evaluation was performed to exclude patients who presented both negative salivary gland biopsy and autoantibodies and who did not fulfil the recently proposed classification criteria [14]. In 80 patients with negative anti-Ro/La autoantibodies, a salivary gland biopsy was not carried out. In these patients, it was not possible to retrospectively evaluate the fulfillment or not of the 2002 classification criteria.

All patients were consecutively included when the fulfillment of criteria was confirmed by our department and thereafter followed up prospectively with regular visits at 6–12 month intervals. Clinical and laboratory data were collected and computerized according to the standard protocol of our department [15, 16]. The individual observation time for every patient was from the time of fulfillment of the 1993 classification criteria until the last hospital visit, transfer out or death. The design of this study conformed to the ethical standards currently applied in Spain. Due to the anonymous nature of the study, informed patient consent was not required.

Systemic involvement was defined as the presence of at least one of the following features [15, 16]: non-erosive arthritis, Raynaud’s phenomenon, lung involvement, nephropathy, vasculitis, peripheral neuropathy or CNS (central nervous system) involvement. Vasculitic involvement was defined as previously described when histological and/or arteriographic confirmation of vascular damage was available [10]. When a cutaneous biopsy was topographically difficult to obtain, it was clinically contraindicated or was not possible due to lacking consent, a diagnosis of vasculitis was made when cutaneous lesions, evaluated by a consultant dermatologist, were considered characteristic of vasculitis and other processes were excluded [10]. B-cell lymphomas were classified according to the 2001 WHO classification for tumours of haematopoietic and lymphoid tissues [17]. Immunological tests were determined as previously described [15, 16].

Statistical analysis

The outcomes measured were development of vasculitic involvement, B-cell lymphoma and death. Possible predictive variables at
the time of SS diagnosis were previous or current parotid enlargement, previous or current vasculitis, parotid scintigraphy grades III or IV [18], positive salivary gland biopsy [13], ANA > 1/80, positive anti-Ro/SS-A and/or anti-La/SS-B, RF > 25 IU/L, positive cryoglobulins (cryocrit > 1%), C3 levels < 0.82 g/l and C4 levels < 0.11 g/l.

Univariate Cox regression analysis was used to evaluate the crude effect of clinical and immunological variables at diagnosis on adverse outcomes. Multivariate Cox regression analysis using a backward stepwise method allowed adjustment for age, gender and the variables that were statistically significant (P < 0.05) in the univariate analysis. The hazard ratios (HRs) and their 95% confidence intervals (CIs) obtained in the adjusted regression analysis were calculated. Kaplan-Meier survival curves were compared using the log-rank and Breslow tests. The statistical analysis was performed with the SPSS program (SPSS, Chicago, IL, USA).

Results

The study cohort included 247 (93%) women and 19 (7%) men with a mean age at the onset of sicca symptoms of 54.7 yrs, a mean age at the time of diagnosis of 56.9 yrs and a total follow-up of 2303 patient-yrs (mean 8.66 yrs).

Development of vasculitic involvement

Twenty-five (9%) patients developed vasculitis after a mean time of follow-up of 58 months (range 12-174). Vasculitis involved the peripheral nerves in 17 patients, the skin in 13, kidneys in three, small bowel in two and pancreas in one. A biopsy specimen was obtained in 20 (80%) patients. The main histological diagnosis was small-vessel vasculitis in 16 (leucocytoclastic in 14 and lymphocytic in two) and medium-sized vessel vasculitis (necrotizing vasculitis) in the remaining four cases.

Univariate Cox regression analysis identified the following variables at diagnosis associated with the development of vasculitis: parotid scintigraphy grades III or IV (HR 4.03, P = 0.025), systemic involvement (HR 3.01, P = 0.007), vasculitis (HR 5.27, P < 0.001), anti-Ro/La antibodies (HR 2.21, P = 0.049), RF > 25 IU/L (HR 2.37, P = 0.034), C3 levels < 0.82 g/l (HR 4.05, P = 0.012), C4 levels < 0.11 g/l (HR 7.53, P < 0.001) and cryoglobulins (HR 5.44, P < 0.001). Multivariate Cox regression analysis identified as independent variables parotid scintigraphy grades III or IV (HR 3.55, P = 0.05) and C4 levels < 0.11 g/l (HR 8.26, P < 0.001) (Table 1).

Table 1. Cox regression analysis of all variables for adverse outcomes (development of vasculitic involvement, B-cell lymphoma and death). Figures are unadjusted (univariate analysis) and adjusted hazard ratios (multivariate analysis including age, gender and the significant variables in the univariate analysis)

<table>
<thead>
<tr>
<th>Variables at diagnosis</th>
<th>Development of vasculitis</th>
<th>Development of B-cell lymphoma</th>
<th>Death</th>
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<tbody>
<tr>
<td></td>
<td>Unadjusted HR (95% CI)</td>
<td>Adjusted HR (95% CI)</td>
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<tr>
<td>Parotid enlargement</td>
<td>1.85 (0.69–4.95)</td>
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<tr>
<td>Parotid scint. III/IV</td>
<td>4.03 (1.19–13.88)</td>
<td>3.55 (1.00–12.62)</td>
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<tr>
<td>Systemic involvement</td>
<td>3.01 (1.35–6.71)</td>
<td>1.53 (0.41–5.72)</td>
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<tr>
<td>Vasculitic involvement</td>
<td>5.27 (2.31–11.99)</td>
<td>2.32 (0.67–8.07)</td>
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<tr>
<td>SGB grades 3 or 4</td>
<td>1.89 (0.25–14.38)</td>
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<tr>
<td>ANA &gt; 1/80</td>
<td>1.10 (0.38–3.24)</td>
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<tr>
<td>Anti-Ro/La antibodies</td>
<td>2.21 (1.00–4.87)</td>
<td>2.02 (0.76–9.69)</td>
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<tr>
<td>RF &gt; 25 IU/L</td>
<td>1.80 (0.25–14.38)</td>
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<tr>
<td>C3 levels &lt; 0.82 g/l</td>
<td>4.05 (1.37–12.03)</td>
<td>1.10 (0.18–6.50)</td>
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<tr>
<td>C4 levels &lt; 0.11 g/l</td>
<td>7.53 (3.28–17.27)</td>
<td>8.26 (3.19–21.49)</td>
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<tr>
<td>Cryoglobulins &gt;1%</td>
<td>5.44 (2.28–13.00)</td>
<td>2.78 (0.78–9.85)</td>
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</table>

Development of B-cell lymphoma

After SS diagnosis, nine (3%) patients developed B-cell lymphoma (eight women and one man, with a mean age at diagnosis of 59.66 yrs).

Univariate Cox regression analysis identified parotid enlargement (HR 6.37, P = 0.006) and C3 levels < 0.82 g/l (HR 7.54, P = 0.016) at diagnosis as variables associated with the development of B-cell lymphoma. Multivariate Cox regression analysis identified C3 levels < 0.82 g/l (HR 7.54, P = 0.016) as an independent variable (Table 1).

Survival

Twenty-five (9%) patients died during follow-up. Twenty were women and five men, with a mean age at death of 72 yrs. The main causes of death were infections in eight, cardiopulmonary diseases in six, vasculitis in three, non-haematological neoplasia in three, lymphoma in two and other causes in three. The standardized mortality ratio (SMR) for the total cohort of patients (adjusted for age and gender with the general Spanish population) was 1.22.

Univariate Cox regression analysis identified the following variables at diagnosis associated with death: systemic involvement (HR 3.62, P = 0.002), vasculitis (HR 5.23, P < 0.001), C3 levels < 0.82 g/l (HR 3.47, P = 0.049), C4 levels < 0.11 g/l (HR 5.52, P < 0.001) and cryoglobulins (HR 5.09, P = 0.001). Multivariate Cox regression analysis identified as independent variables systemic involvement (HR 4.51, P = 0.022), vasculitis (HR 4.58, P = 0.042), C4 levels < 0.11 g/l (HR 4.57, P = 0.027) and cryoglobulins (HR 4.58, P = 0.013) (Table 1).

Prognostic classification

Factors at diagnosis that were statistically associated with an adverse outcome in the multivariate Cox regression analysis were used to postulate a prognostic classification. These were vasculitis, parotid scintigraphy grades III/IV, hypocomplementaemia (low C3 and/or low C4 levels) and cryoglobulinaemia (Table 1). Patients were classified according to the number of these factors present at diagnosis into group A (no factor), group B (1 factor) and group C (2 or more factors). Survival rates for each group were 96%, 93% and 68%, respectively (log rank and Breslow tests < 0.001). Kaplan-Meier plots are shown in Fig. 1. The SMR for each group was 0.75, 1.04 and 6.71, respectively.

Discussion

The natural history of primary SS has been little studied. Some studies performed in small series of patients agree that, although SS is not a benign disease, it is characterized by a steady evolution

\[ \text{Adjusted HR} = \frac{\text{Unadjusted HR}}{\text{Exp}(\text{Adjusted Log HR})} \]
of the predominant symptoms (sicca features and general manifestations) [7, 8, 19, 20]. Two recent studies have prospectively analysed the outcome of primary SS in large series of Greek and Swedish patients [5, 6]. Our study analysed the factors present at diagnosis that were prospectively associated with an adverse outcome (development of vasculitis, B-cell lymphoma or death) in a large cohort of Spanish patients with primary SS.

Nine per cent of our patients developed vasculitis during the follow-up. In primary SS, vasculitis can range from a benign, restricted process to a life-threatening systemic vasculitis [10]. Ioannidis et al. [6] found that the presence of purpura at diagnosis was prospectively associated with a higher risk of mortality, and was thus the first to suggest the prognostic role of vasculitis in the outcome of patients with primary SS. In this study, univariate Cox regression analysis identified severe scintigraphic involvement and positive immunological markers at diagnosis as predictive factors of vasculitis. Parotid scintigraphy was an independent prognostic factor in the multivariate analysis, suggesting that it is not only of diagnostic value, but could also be useful in identifying patients with a high risk of developing extraglandular manifestations.

We have prospectively confirmed retrospective studies [21–23] showing that patients with positive anti-Ro/La antibodies, RF, hypocomplementaemia and cryoglobulins at diagnosis have a higher risk of developing vasculitis during the follow-up. In addition, multivariate analysis confirmed low C4 levels as an independent prognostic factor for vasculitic development. Our results suggest that patients presenting at diagnosis with these immunological markers should be closely followed up due to their higher risk of developing vasculitis.

In this cohort, 3% of patients with primary SS developed a B-cell lymphoma, a similar prevalence to other reports [7, 8, 19, 24–26]. Ioannidis et al. [6] described parotid enlargement, palpable purpura, anti-Ro/La antibodies and low C4 levels as predictors of lymphoproliferation, while the predictive factors found by Theander et al. [27] were vasculitis, low C3, low C4 and CD4+ T lymphopenia. We identified parotid enlargement, low C4, low C3 and vasculitis as predictive factors for development of B-cell lymphoma, although for low C4 and vasculitis the statistical significance was weaker (P-value of 0.05–0.10). These statistical differences between studies may be due to various factors.

The low number of patients developing lymphoma in our study probably explains why some variables showed only a trend to significance. In addition, all three studies included a wide range of lymphoproliferative processes. In spite of these methodological differences, all three studies identified the same factors (parotid enlargement, vasculitis and hypocomplementaemia) as the main predictors of lymphoma development in patients with primary SS.

Previous studies have suggested that some immunological markers at diagnosis may have a key prognostic value in the survival of patients with primary SS. Ioannidis et al. [6] were the first to suggest the prognostic role of low C4 levels, and this was confirmed, together with low C3 levels, by Theander et al. [5]. We also found a prognostic role for low C4 levels at diagnosis, but, in addition, identified cryoglobulins as a new prognostic marker in primary SS. Vasculitis and cryoglobulins were independently associated with mortality in the multivariate analysis, suggesting that the association between hypocomplementaemia and death found in previous studies [5, 6, 28] may be due to the complement activation caused by the cryoglobulinaemic vasculitis that some patients with primary SS may present.

All our patients were included before the introduction of the 2002 AECC (American European Classification Criteria), when salivary gland biopsy and anti-Ro/La autoantibodies were not considered as mandatory criteria. Thus, our cohort includes a subset of patients with negative Ro/La antibodies in whom salivary gland biopsy was not carried out at diagnosis. These patients presented a sicca syndrome unrelated to other processes, together with altered ocular tests and severe involvement in the parotid scintigraphy and with positive immunological markers including ANA and RF, and showed no features suggestive of other systemic autoimmune diseases during the follow-up. Given that, as explained, the 2002 criteria cannot be applied retrospectively in this group of patients, and given that all patients were included homogeneously and had clinical, diagnostic and immunological characteristics only compatible with primary SS, it seems reasonable to us to maintain the homogeneity of the study, rather than exclude one group of patients due to circumstances caused by changes in the fulfilment criteria overtime.

Ioannidis et al. [6] were the first to propose a prognostic classification of patients with primary SS according to the presence of low C4 levels and/or palpable purpura (type I and type II patients). This study has confirmed these data and identified two additional risk factors (severe parotid involvement demonstrated by scintigraphy and cryoglobulinaemia). A survival analysis performed in our cohort according to the presence of these four prognostic factors found that patients with at least two adverse factors had a significantly lower survival rate in comparison with patients with no factor. This suggests that patients who present severe salivary gland involvement, vasculitis, hypocomplementaemia and/or cryoglobulinaemia at diagnosis should be considered as candidates for aggressive therapy. Biological agents, especially those against B-cells (rituximab, epratuzumab, belimumab), may be especially indicated according to recent evidence [29–31]. Future clinical trials should prospectively analyse the possible effect of early administration of these agents on the survival of patients with primary SS with a high risk of developing adverse outcomes.

In summary, the main prognostic factors for an adverse outcome identified in our cohort of patients with primary SS were severe involvement in parotid scintigraphy, vasculitis, hypocomplementaemia and/or cryoglobulins at diagnosis. These features identify a specific subset of patients diagnosed with primary SS in whom a closer follow-up, and probably an earlier and more robust therapeutic management, should be mandatory.

The authors have declared no conflicts of interest.
References