Significance of anti-La/SSB antibodies in primary Sjögren's syndrome patients with combined positivity for anti-Ro/SSA and salivary gland biopsy

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ABSTRACT

Objective. *Immunological parameters exert a relevant diagnostic and prognostic role in primary Sjögren's syndrome (pSS) and may identify specific disease phenotypes. Among disease-associated immunological features, anti-La/SSB are rarely found without concomitant anti-Ro/SSA and their clinical significance in patients with pSS has been poorly investigated. Thus, we aimed to characterise the value of anti-La/SSB analysing clinical and serologic features of a wide cohort of pSS patients with both circulating anti-Ro/SSA and positive salivary gland biopsy (SGB).*

Methods. *Clinical and serological data of 600 pSS patients with both anti-Ro/SSA and SGB positivity and categorised according to anti-La/SSB status were retrospectively analysed. Comparisons between patients with and without circulating anti-La/SSB were performed.*

Results. *Among the whole cohort, 319 (53%) of patients were anti-La/SSB negative and 281 (47%) were anti-La/SSB positive. Anti-La/SSB positive patients were younger at disease diagnosis and had a longer disease duration. Moreover, anti-La/SSB positive patients had a higher prevalence of hypergammaglobulinaemia and circulating rheumatoid factor and of lymphoproliferative disorders in comparison to seronegative group. At multivariate analysis, hypergammaglobulinaemia (OR=1,7; 95% CI 1.17, 2.43), rheumatoid factor (OR=2.3; 95% CI 1.6, 3.3) and lymphoma (OR=2.6; 95% CI 1.12, 5.96) were identified as independent variables significantly associated with anti-La/SSB positivity.*

Conclusion. *In patients with pSS and concomitant anti-Ro/SSA and SGB positivity, the presence of anti-La/SSB may help in identifying a disease subset with distinct prognostic features, especially in terms of higher risk of lymphoproliferative complications.*

Introduction

In the last years, growing awareness of the wide variety of systemic manifestations which may characterise primary Sjögren's syndrome (pSS) prompted the investigation of factors driving the heterogeneity of the disease phenotypes. Although ocular and oral sicca symptoms represent the cardinal features of the disease, data driven by international, multicentre registries showed that more than a quarter of patients may have, sometimes at disease onset, a wide variety of systemic features, often not included in the European SS disease activity index (ESSDAI) classification (1). Immunologic parameters, including anti-Ro/SSA, cryoglobulins or rheumatoid factor, exert a central role, not only in the diagnosis of the disease, but also in characterising disease phenotypes and predicting outcome, in particular lymphoproliferation (2). Among immunological parameters, autoantibodies represent the hallmark of the disease and recent studies highlighted the potential pathogenic and early diagnostic role of some novel tissue specific autoantibodies, such as salivary protein-1, parotid secretory protein and carbonic anhydrase 6 (3). In established disease, on the other hand, anti-Ro/SSA and anti-La/SSB antibodies may be detected in 33-74% and 23-52% of patients, respectively, and characterise a more active clinical and immunologic phenotype with more severe course or worse prognosis (1, 2, 4). Moreover, circulating anti-Ro/SSA and anti-La/SSB antibodies have been associated

with adverse cardiovascular risk profile in cohorts of pSS patients (5-8).
Anti-La/SSB are rarely found without concomitant circulating anti-Ro/SSA and some Authors suggested that isolated anti-La/SSB may be a false-positive reaction reflecting the assay methodology or that they are associated with a disease phenotypically distinct from pSS (9, 10). Consequently, anti-La/SSB have not been included in the recent American College of Rheumatology/ European League Against Rheumatism (ACR/EULAR) set of classification criteria (11). However, the presence of anti-La/SSB appears to have an adjunctive prognostic role in pSS patients, as demonstrated in retrospective analyses of Italian pSS cohorts (12-14).
Few studies have explored the characteristics of isolated anti-La/SSB positivity pSS patients, with conflicting results. The value of existing literature data may be hampered by the use of different methods of antibody detection and by the application of different sets of pSS classification criteria among studies. Moreover, in some studies, minor salivary gland biopsy (SGB), a mandatory criterion in the absence of anti-Ro/SSA and/or anti-La/SSB according to the 2002 American European Consensus Group (AECG) (15), was not performed in all cases (16, 17) and some patients identified as pSS lacked both positive SGB and circulating anti-Ro/SSA and La/SSB. Indeed, SGB has not only a diagnostic value but also a prognostic role in predicting adverse outcomes, such as lymphoma, representing a pivotal exam in the assessment of pSS patients (18).
Thus, in order to better characterise the value of anti-La/SSB in patients with pSS, we analysed clinical and serologic features of a wide pSS cohort, recruited by the Italian Research Group on SS (GRISS), with both circulating anti-Ro/SSA and positive SGB and categorised according to anti-La/SSB status.

Materials and methods

This is a retrospective analysis of a cohort of 1,706 pSS patients fulfilling the 2002 AECG classification criteria (15) and enrolled in the Italian nationwide multicentre database of GRISS. For each patient, all disease-specific manifestations and laboratory markers as well as ongoing and previous therapies were systematically recorded according to a standard form, as previously described (4). Briefly, age at diagnosis and inclusion, history of xerophthalmia, xerostomia, recurrent parotid enlargement, ESSDAI and non-ESSDAI extraglandular manifestations, Raynaud's phenomenon (RP) and lymphoproliferative disorders were collected as clinical data. Disease-specific laboratory markers included leukopenia, low C3 and C4 complement levels, hypergammaglobulinaemia, rheumatoid factor by nephelometry, antinuclear antibodies by immunoflourescent assay, anti-Ro/SSA and anti-La/SSB antibodies by immunoblotting and serum cryoglobulins. For the purpose of the present study, only patients with concomitant circulating anti-Ro autoantibodies and positive SGB, defined as lymphocytic focus score (FS) ≥1 (19), were included. The selected patients were further divided into two groups according to the concomitant presence or absence of distinct positivity of anti-La/SSB antibodies. Demographic, clinical and laboratory characteristics were compared in the two groups.

Statistical analysis

All data were analysed with IBM SPSS Statistics 26.0 (IBM, Armonk, New York, US). For continuous variables, comparisons of median values were carried out with Mann-Whitney U-test. For categorical variables Yates's chi-squared test or Fisher's exact test were performed as appropriate. In order to account for type one error, Bonferroni correction was calculated (α=0.05, 17 comparisons) and data were considered significant for $p\leq 0.003$. Multivariate logistic regression was performed on variables significant at univariate analysis.

Results

A total of 600 pSS patients (95% female) with both SGB and anti-Ro/SSA positivity were selected from the original cohort and included in the analysis. The median age at diagnosis was 50 years (range 10–86) and the median disease duration was 5 years (range 0-45). Of these, 319 patients were anti-La/SSB negative and 281 anti-La/SSB positive. Demographic, clinical and laboratory features of the whole population are reported in Table I. Anti-La/SSB positive patients were younger at disease diagnosis and had a longer disease duration in comparison to patients without circulating anti-La/SSB. Among the serologic variables, the group with evidence of circulating anti-La/SSB had a higher prevalence of hypergammaglobulinaemia and circulating rheumatoid factor in comparison to group without evidence of anti-La/SSB. Interestingly, the prevalence of lymphoproliferative disorders was higher in patients with anti-La/SSB in comparison to anti-La/SSB-negative patients (Table I). The adjusted multivariate analysis identified hypergammaglobulinaemia (OR=1,7; 95% CI 1.17, 2.43; p=0.005), rheumatoid factor (OR=2.3; 95% CI 1.6, 3.3; p=0.0001) and lymphoma (OR=2.6; 95% CI 1.12, 5.96; p=0.026) as independent variables.

Discussion

The aim of this study was to examine the impact of anti-La/SSB positivity on a well-characterised cohort of patients with both circulating anti-Ro/SSA and positive SGB, thus satisfying all sets of pSS classification criteria. Interestingly, we found that, in patients with anti-Ro/SSA positivity, the concomitant presence of anti-La/SSB further characterises subjects with a younger age at diagnosis and a longer disease duration, along with a significant higher prevalence of hypergammaglobulinaemia, rheumatoid factor and, interestingly, of nearly three-fold higher risk of lymphoma.
The autoantibody status represents a main factor driving the phenotypic expression of pSS and may help in the identification of subgroups of patients at poorer prognosis (3). Indeed, anti-Ro/SSA autoantibodies are highly prevalent in pSS patients and identify a disease subset clearly different from anti-Ro/SSA negative subjects (20). Several studies confirmed that anti-Ro/SSA positivity, independently of anti-La/SSB status, is associated with a more active phenotype, usually characterised

Table I. Clinical and serological features in the whole pSS cohort with SGB and anti-Ro/SSA positivity and in groups categorised according to concomitant anti-La/SSB status. Continuous variables are shown as median (min – max). Categorical variables are shown as number of subjects (%). Results are considered significant for $p \leq 0.003$.

	All n=600	Anti-La/SSB - n=319	Anti-La/SSB +n=281	*p* (Anti-La/SSB+ *vs.* Anti-La/SSB-)
Demographic features				
Age at diagnosis (years)	50 (10-86)	52 (11-86)	48 (10-83)	**0.002**
Disease duration (years)	5 (0-45)	4 (0-33)	6 (0-45)	**< 0.0001**
Gender (female)	572 (95%)	305 (95.6%)	267 (95.0%)	0.881
Clinical features				
Xerophtalmia	553 (92%)	294 (92%)	259 (92%)	1.000
Xerostomia	548 (91%)	291 (91%)	257 (91.5%)	1.000
Parotid swelling	205 (34%)	96 (30.1%)	109 (38.8%)	0.031
Articular	382 (64%)	208 (65.2%)	174 (61.9%)	0.454
Purpura	57 (9.5%)	26 (8.2%)	31 (11.1%)	0.282
Raynaud's phenomenon	147 (24.5%)	80 (25.1%)	67 (23.8%)	0.798
Extra-glandular manifestations	282 (47%)	138 (43%)	144 (51%)	0.059
Lymphoma	33 (5.5%)	8 (2.5%)	25 (8.9%)	**0.001**
Laboratory features				
Low complement	134 (22%)	67 (21.0%)	67 (23.8%)	0.462
Leukopenia	178 (30%)	82 (25.7%)	96 (34.2%)	0.030
Hypergammaglobulinaemia	356 (59%)	159 (49.8%)	197 (70.1%)	**< 0.0001**
Monoclonal component	41 (7%)	14 (4.4%)	27 (9.6%)	0.018
Rheumatoid factor	372 (62%)	160 (50.2%)	212 (75.4%)	**< 0.0001**
Cryoglobulinaemia	26 (4%)	9 (2.8%)	17 (6.0%)	0.082

by younger age at diagnosis, longer disease duration, recurrent glandular swelling, more active immunological profile, severe salivary and ocular hypofunction, extra-glandular involvement and higher prevalence of systemic non-ESSDAI features (1, 2, 9, 16, 21, 22). The subset of patients with isolated positive anti-La/SSB antibodies seem to be characterised by younger age at diagnosis, higher prevalence of xerophthalmia, but lower impairment of lacrimal and salivary function and lower lymphocytic glandular infiltration in comparison to the other groups (9, 10, 17). However, the few studies analysing this subset of patients included a very high percentage of anti-Ro/SSA and anti-La/SSB double negative patients, as high as 65%, and relatively low rates of available or positive SGB, which implies that a significant proportion of patients did not satisfy the AECG classification criteria, arising questions regarding the accuracy of pSS diagnosis in a subset of the included subjects (9, 16). Additionally, in some studies, both 2002 AECG or ACR 2012 classification criteria were allowed, eventually causing an enrolment of patients with heterogeneous characteristics (9, 10). Finally, most studies employed ELISA to detect the presence of anti-Ro/SSA and anti-La/SSB autoantibodies, which, in fact, is a very sensitive technique but not as specific, thus potentially resulting in a significant rate of low levels anti-La/SSB positivity with no clinical significance (23).

To our knowledge, this is the first study focusing on a very selected and well characterised population with both positive anti-Ro/SSA and SGB, thus limiting the potential impact of subject heterogeneity on data interpretation.

A younger age at diagnosis of anti-La/SSB positive patients is in line with a recent study demonstrating that pSS patients with early-onset disease, defined as age at onset ≤ 35 years, display a significant higher prevalence of anti-Ro/SSA and anti-La/SSB antibodies in comparison to the later onset group, thus suggesting a possible direct pathogenic role of these antibodies (24). These results deserve consideration and reinforce the hypothesis that anti-La/SSB may have a prognostic value in the assessment of pSS patients (25, 26).

Similarly, our finding concerning a higher prevalence of lymphoma in patients with positive anti-La/SSB antibodies, are in accordance with multiple studies reporting an association between anti-La/SSB and a more severe glandular involvement. In particular, in a cohort of anti-Ro/SSA^{+} patients, concomitant anti-La/SSB positivity was significantly associated with a FS >1 (28). Additionally, in a recent analysis of more than 10,000 pSS enrolled in the Big Data Project, the subgroup of subjects with isolated anti-La/SSB positivity displayed the highest frequency of active glandular ESSDAI domain in comparison to patients with isolated anti-Ro/SSA or carrying both antibodies (17). This may suggest that the development of immunoreactivity to La/SSB antigen may drive the inflammatory infiltration of exocrine glands and directly contribute to tissue damage (27, 29). In this setting, the prognostic value of glandular inflammatory infiltrate as a marker of lymphoproliferative risk (18, 30) and the demonstration that circulating anti-La/SSB autoantibodies are associated with cryoglobulinaemia, cryoglobulinaemic vasculitis and higher risk of B-cell lymphoma in retrospective analyses of a similar Italian cohort (12-14, 31) suggest an intriguing relationship between La/SSB antigen, glandular damage and lymphoproliferative risk worth of further studies. Indeed, the increased expression of La/SSB messenger RNA (mRNA) in the cytoplasm of SG ductal epithelial cells may contribute to the antigen-driven glandular immune response and elicit the systemic antibody production (32).

In agreement with the aforementioned data, anti-La/SSB positivity was also associated with higher levels of circulating immunoglobulins and rheumatoid factor which are recognised prognostic markers of a more active systemic disease and are both closely correlated to immunological features suggesting a higher lymphoproliferative risk, such as cryoglobulins or lymphopenia (17, 21, 33), and with positive SGB (28). Interestingly, serum levels of chemokine (C-X-C motif) ligand 13 (CXCL13), a marker of lymphoproliferative risk in pSS, have been recently demonstrated to correlate with immunoglobulin G, rheumatoid factor, anti-Ro/SSA and anti-La/SSB positivity in a cohort of pSS patients with lymphoma (34).

In conclusion, our study design allowed for an utterly precise evaluation of the impact of anti-La/SSB positivity in terms of clinical and immunological disease features in a large cohort of patients. Interestingly, we found that anti-La/SSB positivity in pSS patients is associated with younger age at diagnosis, longer disease duration and a higher prevalence of lymphoma and hypergammaglobulinaemia. Although anti-La/SSB status was excluded from the latest 2016 ACR-EULAR classification criteria, we believe its positivity does indeed identify a subset of patients with distinct features, especially in terms of higher risk of lymphoproliferative complications. Therefore, anti-La status may still be of utmost clinical value in terms of patient prognostic stratification and, in turn, a tailored follow-up schedule.

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