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Biomarkers of lymphoma in Sjögren's syndrome and evaluation of the lymphoma risk in prelymphomatous conditions: Results of a multicenter study

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ABSTRACT

Objectives: To define the biomarkers associated with lymphoproliferation in primary Sjögren's syndrome (pSS) by distinguishing in separate groups the two best-recognized non-malignant prelymphomatous conditions in pSS, i.e., salivary gland swelling and cryoglobulinemic vasculitis (CV).
Methods: A multicenter study was conducted in 5 centres. Patients fulfilled the following criteria: (1) positive AECG criteria for pSS, (2) serum cryoglobulins evaluated, and (3) lack of hepatitis C virus infection. Four groups were distinguished and analysed by multinomial analyses: (1) B-cell non-Hodgkin's lymphoma (NHL), (2) CV without lymphoma, (3) salivary swelling without NHL (SW), and (4) pSS patients without NHL or prelymphomatous conditions.
Results: Six hundred and sixty-one patients were studied. Group 1/NHL comprised 40/661 (6.1%) patients, Group 2/CV 17/661 (2.6%), Group 3/SW 180/661 (27.2%), and Group 4/pSS controls 424/661 (64.1%). Low C4 [relative-risk ratio (RRR) 8.3], cryoglobulins (RRR 6.8), anti-La antibodies (RRR 5.2), and leukopenia (RRR 3.3) were the variables distinguishing Group 1/NHL from Group 4/Controls. As concerns the subset of patients with prelymphomatous conditions, the absence of these biomarkers provided a negative predictive value for lymphoma of 98% in patients with salivary swelling (Group 3/SW). Additional follow-up studies in patients with SW confirmed the high risk of lymphoma when at least 2/4 biomarkers were positive.
Conclusions: Lymphoma-associated biomarkers were defined in a multicentre series of well-characterized patients with pSS, by dissecting the cohort in the pSS-associated prelymphomatous conditions. Notably, it was demonstrated for the first time that among the pSS patients with salivary swelling, only those with positive biomarkers present an increased risk of lymphoma evolution.
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1. Introduction

Primary Sjögren's syndrome (pSS) is an autoimmune and lymphoproliferative disorder primarily involving the salivary and lachrymal glands, leading to glandular damage, dysfunction and sicca syndrome [1,2]. Lymphoma occurs in about 5% cases, and it is the main cause of a decreased survival in pSS [3,4].

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Different risk factors for lymphoma evolution have been described in pSS [4–6]. Cryoglobulinemic vasculitis and salivary gland/parotid swelling, in particular, have been repeatedly reported to predispose to lymphoma [4,7–11], although specifically designed follow-up studies are lacking. In previous studies dealing with lymphoma risk in pSS, however, the patients had been distinguished into two main groups, i.e., with or without lymphoma. Patients with lymphoma present a cryoglobulinemic vasculitis and/or a salivary a gland/parotid swelling more frequently than pSS patients lacking lymphoma [12]. However, since it is now well-recognized that pSS patients without lymphoma but with cryoglobulinemic vasculitis and/or salivary gland/parotid swelling may evolve into lymphoma with greater frequency, and since biologic studies also indicate these pictures as more advanced stages of lymphoproliferation [10,13], cryoglobulinemic vasculitis and salivary gland/parotid swelling in the lack of lymphoma can be well considered as prelymphomatous conditions in pSS [11].

These prelymphomatous conditions should be, however, analysed separately, when evaluating lymphoma risk in pSS, to more properly define the risk of lymphoma evolution in different subsets of the disease. The study of a large number of patients, possibly coming from different Centres, would be important to this end. Of note, while cryoglobulinemic vasculitis is rare but more strictly associated with lymphoma in pSS, glandular swelling is more common, though fewer patients develop lymphoma [14]. On the other hand, pSS is primarily a disorder of mucosa-associated lymphoid tissue (MALT), and pSS-associated cryoglobulinemia appears related to MALT lymphoproliferation [15]. Furthermore, among the subset of pSS patients with parotid swelling, integrated clinicopathological and molecular follow-up studies showed that the lymphoma risk is higher when myoepithelial sialadenitis (MESA) presents more aggressive pathologic features and the persistence of tissue monoclonal B-cell expansion in metachronous biopsies [10,11].

Finally, besides the distinction of pSS with prelymphomatous lymphoproliferation as a separate group, the concomitant presence of infection by the hepatitis C virus (HCV) should also be assessed. Data interpretation would be more difficult if HCV-positive subjects are not separated.

The aim of this study was then to investigate the laboratory biomarkers associated with lymphoproliferation in pSS in a large multicentre study by clearly differentiating patients with prelymphomatous conditions (i.e., cryoglobulinemic vasculitis and salivary gland/parotid swelling) as separate groups, to better evaluate the risk of lymphoma progression in different pSS subsets. A cohort of 1170 Italian pSS patients was considered, studying all the patients who satisfied the American European Consensus Group pSS criteria [16], who had been repeatedly evaluated for cryoglobulins in the serum, and who had all been tested for HCV, being negative for it.

Secondly, the selected biomarkers were investigated in the subset of pSS with prelymphomatous conditions. Of note, it was demonstrated for the first time that among the pSS patients with salivary swelling, only those with positive biomarkers presented an increased risk of lymphoma evolution, while cryoglobulinemic vasculitis in SS cannot be differentiated from lymphoma in pSS by using the biomarkers.

2. Patients and methods

2.1. Study design and enrolment criteria

An observational, retrospective, cross-sectional multicentre database involving five Italian reference centres for pSS was considered. A database of 1170 patients pSS from four Rheumatology centres [17] was reviewed.

In this database, all patients fulfilled four or more of the preliminary diagnostic criteria for SS proposed by the European Community Study Group in 1993 [18]. Database data collected have been published, and, briefly, include age at diagnosis, age at inclusion, cumulative clinical and immunologic features, sicca symptoms, presence of salivary gland enlargement defined as persistent swelling or episodes of parotid or submandibular swelling lasting at least two months [10,11], and signs or symptoms of extraglandular involvement. The laboratory abnormalities recorded include leukopenia, levels of C3 and C4 complement, hypergammaglobulinemia, rheumatoid factor, antinuclear antibodies (ANA), anti-Ro/SSA antibody, anti-La/SSB antibody, serum cryoglobulins [19], thyroid function tests with antithyroid autoantibodies, and hepatitis C and B serology.

For the present study, the inclusion criteria for pSS patients within the aforementioned database were as follows.

a. Fulfilment also of the American European Criteria for the classification of pSS [16].
b. Recording of repeated tests for the detection of serum cryoglobulins (at least two tests in a 12-week interval) [20].
c. Recording of the negativity for anti- HCV antibodies assessed by ELISA test.

For the inclusion, all the above criteria had to be satisfied.

Patients were subsequently categorized into four groups defined as follows: (1) patients with lymphoma (including lymphoma patients with concomitant cryoglobulinemic vasculitis and/or salivary gland swelling) (Group 1/NHL); (2) patients with cryoglobulinemic vasculitis, as previously defined in detail [20,21] without lymphoma (Group 2/CV); (3) Patients with salivary gland swelling without lymphoma, with or without concomitant cryoglobulinemic vasculitis (Group 3/SW); and (4) pSS patients without lymphoma and without cryoglobulinemic vasculitis or salivary gland swelling (Group 4/pSS controls).

The serological biomarkers investigated in the four Groups in this analysis were the following: presence or absence of antinuclear antibodies, anti-SSA/Ro, anti-SSB/La, low C3, low C4, rheumatoid factor, hypergammaglobulinemia, serum monoclonal component, leukopenia, and serum cryoglobulins.

The biomarkers associated with lymphoma in pSS were finally investigated as predictors of lymphoma development also in 41 database pSS patients with glandular swelling followed prospectively, by comparing 22 pSS patients who developed an overt lymphoma in the follow-up with 19 consecutive pSS patients with definitely non-malignant salivary gland swelling, i.e., with histopathological evidence of MESA after tissue biopsy, and who did not develop lymphoma during a follow-up of at least 5 years after tissue biopsy.

2.2. Statistical analysis

Data were expressed as mean ± standard deviation for continuous variables and as absolute frequencies and percentages for nominal variables. Primary endpoint was investigated by using univariate and multivariate multinomial stepwise logistic analyses. Group 4/pSS controls was assumed as “reference group” in both univariate and multivariate comparisons and, on this basis, the relative-risk ratios (RRR) of belonging to each of the other three groups (Group 1/NHL, Group 2/CV, Group 3/SW) were then computed for the serological biomarkers.

Variables associated to the Groups with p values <0.1 by univariate analysis were entered in a final model. The variables

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