



Original Article

Usefulness of Antibodies and Minor Salivary Gland Biopsy in the Study of Sicca Syndrome in Daily Clinical Practice[☆]



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ABSTRACT

Objectives: To assess the association between histologic findings in the minor salivary gland biopsy (MSGB) and anti La (La/SS-B) and antiRo antibodies (Ro/SS-A), antinuclear antibodies (ANA) and rheumatoid factor (RF), and compare the value of the latter as diagnostic tests with MSGB, considered as the gold standard.

Materials and methods: Patients with suspected primary Sjögren syndrome (PSS) referred for MSGB were included. Antibody measurements were performed. Grades III and IV biopsy results were considered positive.

Results: Two hundred and eighteen (218) patients were included, 95% females, with a median age of 54 years and 12 months median duration of sicca symptoms. Thirty-six of the biopsies were positive. 33% of patients had positive anti Ro/SS-A anti La/SS-B antibodies, 62% had positive ANA, and 31% positive RF. A statistically significant association was found between MSGB and anti Ro/SS-A anti La/SS-B, ANA and RF. ANA were the most sensitive antibodies (84%. 95% CI: 75–92), and the most specific were: anti Ro/SS-A and/or anti La/SS-B (78%. 95% CI: 71–85) and RF (78%. 95% CI: 69–87).

Conclusion: On PSS clinical suspicion, anti Ro/SS-A and anti La/SS-B antibodies have a great value to achieve the diagnosis, with MSGB useful for diagnosis of seronegative patients. The results also suggest the importance of ANA and RF for PSS classification.

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Utilidad de los anticuerpos y de la biopsia de glándula salival menor en el estudio del complejo sicca en la práctica diaria

RESUMEN

Objetivos: Evaluar la asociación entre los hallazgos histológicos de la biopsia de glándula salival menor (BGSM) y los anticuerpos anti La (La/SS-B), anti Ro (Ro/SS-A), anticuerpos antinucleares (FAN) y factor reumatoideo (FR), y comparar el valor de estos como test diagnóstico con la BGSM considerada como patrón oro.

Material y métodos: Se incluyeron pacientes con sospecha de síndrome de Sjögren primario (SSp) derivados para realización de BGSM. Se realizó medición de anticuerpos y se consideró BGSM positiva a los grados III y IV de la clasificación de Chisholm.

Resultados: Se incluyeron 218 pacientes, 95% género femenino, con una mediana de edad de 54 años y de tiempo de evolución de los síntomas sicca de 12 meses. El 36% de las biopsias fueron positivas. El 33% de los pacientes presentaban anticuerpos anti Ro/SS-A anti La/SS-B positivos, 62% FAN positivo y el 31% FR positivo. Se encontró asociación estadísticamente significativa entre la BGSM y anti Ro/SS-A, anti La/SS-B, FAN y FR. El FAN resultó ser el anticuerpo más sensible (84% IC95%: 75-92), siendo los más específicos: anti Ro/SS-A y/o anti La/SS-B (78% IC95%: 71-85) y el FR (78% IC95%: 69-87).

Palabras clave:

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Conclusión: Ante la sospecha clínica de SS, los anticuerpos anti Ro/SS-A y anti La/SS-B son de gran valor para arribar al diagnóstico, siendo la BGSMB especialmente útil en los pacientes seronegativos. Los resultados también sugieren la utilidad del FAN y el FR para la clasificación de SS.

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Introduction

Sjögren's syndrome (SS) is a systemic autoimmune disease involving the exocrine glands, manifesting with symptoms arising from hyposalivation thereof. In addition to symptoms arising from the exocrine affection, the disease can produce various extraglandular manifestations. SS can occur alone, as primary SS (pSS) or associated with other autoimmune diseases, as secondary SS.¹

To date different classification criteria have been proposed, which are based on a combination of clinical, serological and histological findings.^{2–8}

Histology, as part of the diagnosis, was first proposed in 1970 by Waterhouse, Chisholm and Mason; the latter were those establishing the score using foci of inflammatory cells aggregates.⁹

In order to obtain the material for pathology, a minor salivary gland biopsy (MSGB) is performed. While this is an invasive procedure, it is easy to perform and several studies show a low frequency of complications, which are usually mild.^{8–14}

However, despite the simplicity of the technique, MSGB is not incorporated into daily practice in all centers, which leads to inconvenience in defining the presence of SS according to the American–European 2002 classification criteria currently in force.⁸

According to these criteria, the presence of a compatible MSGB and/or the presence of anti-Ro/SS-A and/or anti La/SS-B are necessary to diagnose pSS.

Furthermore, the 1993 European criteria and⁷ the 2012 preliminary criteria¹⁰ include, in addition to anti Ro/SS-A and La/SS-B antibodies, anti-nuclear (ANA) and rheumatoid factor (RF) as part of the serological criteria.

Because there is still difficulty in obtaining a MSGB for the diagnosis of SS in daily practice, we set out to estimate the association between the presence of histological stages III and IV affection in the classification proposed by Chisholm and the presence of anti Ro/SS-A and anti-La SS-B; and assess the value of these antibodies as a diagnostic test, compared with MSGB, which was taken as a reference test or gold standard.

The secondary objectives evaluated were the association between the presence of infiltrates stages III and IV in MSGB with ANA and RF positivity and analyze the value of such antibodies as a diagnostic test, compared with MSGB.

Materials and methods

The study design was observational, analytical and cross-sectional.

We included consecutive patients with suspected pSS derived from different centers of Argentina to the Rheumatology Department, Hospital Rivadavia, for a MSGB, between October 2007 and December 2011.

Exclusion criteria were related to the procedure: use of aspirin or other NSAIDs within the week before the study, clinical signs of local infection at the site of the biopsy, patients with anticoagulation or a clotting disorder or other causes of sicca symptoms and treatment with anticholinergic drugs or radiotherapy of the head and neck. Biopsies in which the material obtained was insufficient or non-glandular, patients with other autoimmune associated rheumatic disease, cases where results of anti-Ro/SS-A or

anti-La/SS-B were not available were also excluded as well as those who refused inclusion into the protocol.

Demographics (age, gender), duration of sicca symptoms when performing the biopsy, concomitant disease (hypothyroidism and diabetes), treatment at the time of the biopsy (corticosteroids, immunomodulatory/immunosuppressive drugs), antibody results (ANA in Hep 2, anti Ro/SS-A, anti-La/SS-B by ELISA, latex nephelometry and turbidimetry RF,) as well as MSGB results according to the classification proposed by Chisholm–Mason were recorded. The results of biopsies stages III and IV were considered as positive 9.

Xerophthalmia and xerostomia were defined as the presence of symptoms of ocular and oral dryness according to the classification criteria proposed in 2002.⁸

Since the 2002 classification criteria require positivity for anti Ro/SS-A and/or anti La/SS-B or a positive MSGB to classify a patient with pSS and the latter being an invasive biopsy procedure, we decided to choose the latter as the gold standard, with the objective of assessing the value of the antibodies and their usefulness as a replacement for MSGB.

The pathologic study was carried out by a single, independent and blinded pathologist, the Chair of Anatomic Pathology at the Faculty of Medicine of Buenos Aires, with over 15 years experience in the evaluation of histological material from MSGB. Antibodies were determined in different centers of reference of the country, mainly in the city of Buenos Aires, and the cutoff used to define the results as positive or negative was defined by the laboratory of each center.

The study was approved by the education, research and ethics committee of the hospital. Patients signed informed consent.

Statistical analysis

The data were fed into a Microsoft Excel database and analyzed using the STATA 11 statistical package.

The general characteristics of the population were described; continuous variables were reported as means and standard deviations (SD) or medians and interquartile ranges (IQR) according to their distribution. Frequency distribution analysis of categorical variables was performed.

For the bivariate analysis a *t* test or Mann–Whitney test for continuous variables, such as distribution and sample size, was used. Categorical variables were analyzed using chi-square or Fisher exact test according to a distribution table as expected frequency.

To assess the association and the presence of potential confounders in the relationship between the positivity of each of the antibodies and MSGB, three models of multiple logistic regression were performed: 1–MSGB and anti Ro/SS-A, anti-La/SS B antibodies, 2–MSGB and ANA and 3–MSGB and RF, considering the biopsy as the dependent variable. Odds ratios (OR) and corresponding 95% CI were calculated.

$P < .05$ was considered as significant.

Sensitivity (S), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV) and positive likelihood ratio (PLR) were calculated with their respective 95% confidence intervals (95%CI) for each antibody and compared with MSGB, which was taken as the gold standard.

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