CONCISE REPORT

B cell MALT lymphoma diagnosed by labial minor salivary gland biopsy in patients screened for Sjögren's syndrome

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Case report: Three patients presented to the Sjögren's syndrome (SS) Clinic at the National Institute of Dental and Craniofacial Research for screening. The records of patients with SS with a diagnosis of lymphoma were examined to determine whether the diagnosis was made in any of the cases as a result of labial salivary gland (LSG) biopsies. All patients had typical features of primary SS according to the American-European Consensus Group criteria. B cell mucosa associated lymphoid tissue (MALT) lymphoma was diagnosed based upon the LSG biopsy.

Conclusion: This report underlines the advantages of performing LSG biopsies as a routine part of screening for SS, and shows that it may in some instances lead to early diagnosis of MALT lymphomas in patients who show no signs of pre-existing lymphoma.

Sjögren's syndrome (SS) is an autoimmune exocrinopathy characterised by decreased lachrymal and salivary gland function, resulting in keratoconjunctivitis sicca and dry mouth.[1] Lymphocytic infiltration in these glands is a major feature of SS. These infiltrates consist of mononuclear cells, which penetrate the glandular epithelial tissue and are called benign lymphoepithelial lesions.[2] One of the criteria for classification of SS includes the presence of ⩾1 foci of 50 or more lymphocytes (a focus) within a 4 mm^2 field[3] in a labial salivary gland (LSG) biopsy specimen.

SS generally follows a rather indolent course, but development of malignant lymphoma may occur.[4] It has been estimated that patients with SS have an up to 44 times increased risk of developing lymphoma[5] compared with the general population. Lymphoma has been reported in 4.3% of patients with SS.[6] In most cases, this is a low grade B cell lymphoma of the mucosa associated lymphoid tissue (MALT) type. Thus far, lymphoma has been diagnosed in patients with SS with atypical or persistent parotid or submandibular salivary gland swelling. Biopsy or resection of the affected gland histopathologically confirmed the diagnosis of B cell MALT lymphoma.[7–10]

In this article, we report on three patients who were screened for SS. Each was found to have a MALT lymphoma upon labial minor salivary gland biopsy. None of the patients appeared to have pre-existing lymphoma, fever, night sweats, or persistent major salivary gland swelling at the time of evaluation.

CASE REPORTS

Case 1

Patient 1, a 53 year old white woman, presented with a 2.5 year history of oral and ocular dryness, which began precipitously with an episode of sun exposure and photosensitive rash. This was accompanied by generalised inflammation and swelling of the extremities. Subsequently, she had an unintentional weight loss of 9 kg and was referred to an oncologist, who found no apparent cause for this loss of weight. Her review of symptoms was significant for Raynaud's phenomenon, vasculitis, shortness of breath on climbing stairs, and swelling of the legs, feet, and ankles.

Upon physical examination, the patient had multiple non-blanching purpuric lesions on the lower limbs. The conjunctivae were injected, and there was no salivary gland enlargement or lymphadenopathy. Upon examination of the blood samples, the alkaline phosphatase (192 U/l), glutamic pyruvic transaminase (53 U/l), glutamic oxalacetic transaminase (48 U/l), total protein (84 g/l), IgG (17.00 g/l), IgM (8.04 g/l), C reactive protein (10.5 mg/l), and erythrocyte sedimentation rate (ESR; 72 mm/1st h) were raised, while C4 (<0.1 g/l) levels were decreased. Additionally, the antinuclear antibodies (ANA), anti-SSA, and anti-ribonucleoprotein antibody tests were positive. She had keratoconjunctivitis sicca by both Van Bijsterveld score on ocular dye staining and the Schirmer I test. A minor salivary gland biopsy disclosed extranodal marginal zone B cell lymphoma of the MALT type, expressing monoclonal κ light chain and CD43 coexpression. The infiltrate was focally positive for CD20; the neoplastic cells were CD3 negative.

The patient was then referred for bone marrow aspirate and biopsy, which showed localisation of non-Hodgkin's lymphoma. A positron emission tomography scan showed a focal area of intense tracer uptake in the right chest area that appeared to be near the pleural pericardial surface on the right anteriorly, which could represent lymphoma.

Case 2

Patient 2, a 51 year old Middle Eastern woman, presented with oral dryness complaints of 1 year's duration and 3 years of ocular dryness. The patient had a history of intermittent swelling of the parotid glands, approximately two episodes a year, for the past 3–4 years. She had a history of smoking with chronic hoarseness. There was no history of unintentional weight loss or vasculitis.

Blood tests showed raised levels of total protein (92 g/l), amylase (167 U/l), IgG (28.40 g/l), IgA (4.74 g/l), IgM (2.41 g/l), rheumatoid factor (473 IU/ml) and a raised ESR (70 mm/1st h), while C4 levels (0.10 g/l) and white blood cell count (2.54×10^9/l) were decreased. Additionally, the ANA, anti-SSA, and anti-SSB antibody tests were positive. The patient had keratoconjunctivitis sicca, as shown by both the Schirmer I test and Van Bijsterveld score on ocular dye staining. The salivary flow was decreased and met SS flow requirements according to the American-European criteria. The minor salivary gland biopsy revealed an atypical lymphoid infiltrate, expressing excess κ light chains and suspicious of involvement of the extranodal marginal zone B

Abbreviations: ANA, antinuclear antibodies; ESR, erythrocyte sedimentation rate; LSG, labial salivary gland; MALT, mucosa associated lymphoid tissue; SS, Sjögren's syndrome

cell lymphoma of the MALT type. The patient was then referred to oncology for staging of her lymphoma.

Case 3

Patient 3, a 55 year old woman, presented with a 25 year history of SS. She complained of dryness of the mouth, skin, nose, and vagina, as well as a gritty and sandy feeling in her eyes. She had had an episode of vasculitis on her upper arms and a history of fatigue. She had experienced frequent, intermittent swelling of the parotid glands for the past 20 years, which had been well controlled with 5 mg prednisone daily. Her history was significant for hypothyroidism, shingles, and oral and genital herpes. Six years before the current evaluation she had non-Hodgkin's lymphoma of the right groin, which went into complete remission after chemotherapy.

Upon examination of the blood the ANA, rheumatoid factor, and anti-SSA antibody titres were positive, and the ESR (81 mm/1st h) was raised. Keratoconjunctivitis sicca was confirmed by an increased Van Bijsterveld score on ocular dye staining as well as by the Schirmer I test and she met salivary flow requirements according to the American-European criteria. A minor salivary gland biopsy showed a marginal zone B cell lymphoma of the MALT type, expressing monoclonal λ light chains. She was then referred to her physician for staging of the MALT lymphoma and treatment was started with Leukeran (4 mg daily) and her prednisone was increased to 20 mg/day.

DISCUSSION

Described here are three middle-aged women, who presented to the clinic with typical features of primary Sjögren's syndrome on first evaluation. Each patient had subjective complaints and objective evidence of ocular and oral dryness according to the American-European Consensus Group criteria and were all ANA and anti-extractable nuclear antigen positive (anti-SSA, anti-SSB, and/or anti-RNP antibodies). Patients 1 and 2 both had low C4 levels, which have been associated with an increased risk for development of lymphoma in patients with SS.[10] Two of the three patients had no pre-existing lymphoma, in contrast with the third patient who had a history of non-Hodgkin's lymphoma that appeared to be in remission. All three patients were diagnosed with a marginal zone B cell MALT lymphoma with monoclonal light chain expression upon LSG biopsy.

MALT is normally found in Peyer's patches in the ileum of the lower gastrointestinal tract, where it has an important role in the normal humoral immune response. Mononuclear cell lymphocytic infiltrates in the exocrine glands can develop into marginal zone B cell lesions or acquired MALT. These infiltrates are still benign and functional. However, patients with SS have an increased risk of developing monoclonal B cell MALT lymphoma. It has been suggested that prolonged autoimmune inflammation as in SS or persistent antigenic stimulation due to for instance to *H pylori* and human herpes virus infection may play a part in the development of lymphoma.[11 12]

It has been recently shown that the level of circulating BAFF (BLyS, TALL-1, THANK, zTNF4) correlates with the level of autoantibodies in human SS. BAFF is a B cell activating factor, which regulates B cell differentiation and proliferation. It is considered to have a pathogenetic role in activating specific autoreactive B cells and modulating the level of production of autoantibodies which are diagnostic criteria of SS.[13] Now shown is that a spectrum of B cell tumour cells express BAFF and BAFF receptors. The research indicates that these B cells deregulate an otherwise physiological autocrine survival pathway and evade apoptosis.[14] Under high B cell activity, marginal zone B cells may form germinal centres in the salivary glands of some patients with SS, which could give rise to oligoclonal populations of B cells, possibly resulting in MALT lymphoma.[15] Conceivably, diminution of inflammation through immunomodulatory treatment might play a role in the prevention and treatment of lymphoma in SS, similar to the effects of elimination of antigenic stimulation by eradication of *H pylori*, leading to regression of the MALT lymphoma.

LSG biopsies, aside from being a part of the SS diagnostic criteria, can offer clues to the presence of a lymphoma. Biopsies should be carefully evaluated for lymphoma, especially when the mononuclear cells have a uniform appearance. Histologically, they can show atypical plasmacytoid cells and Dutcher bodies. Upon suspicion, the specimen should be immunohistochemically stained to determine the presence of polyclonal plasmacytosis for confirmation of the final diagnosis. Further research may clarify the potential role of measuring BAFF levels in these biopsy specimens as a marker for increased risk of lymphoma in patients with SS.

The present report describes three patients who presented as typical patients with SS, but who were diagnosed with MALT lymphoma only on their labial minor salivary gland biopsy. These findings underline the need for degree of awareness of the possibility of lymphoma in patients with features of SS. By performing LSG biopsies routinely as a part of screening, lymphomas which might otherwise escape detection can be found.

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