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Clinical, histopathological and immunohistological study of lymphoid disorders in the parotid gland of patients with Sjögren's syndrome

Klinička, morfološka i imunohistohemijska analiza limfoidnog poremećaja u parotidnoj žlezdi kod bolesnika sa Sjegrenovim sindromom

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Abstract

Bacground/Aim. Sjögren's syndrome is a chronic autoimmune systemic disease characterized by polyglandular tissue destruction, leading to keratoconjunctivitis sicca and xerostomia. These patients have 44-fold increased risk of developing salivary gland lymphoma, of which 80% are marginal zone (MALT) type. Having in mind that criteria for distinguishing benign lymphoepithelial lesions from MALT lymphoma are obscure, the aim of this study was to provide practical information that could be integrated into diagnostic practice. **Methods.** Among 32 parotidectomies, 27 cases were identified as having benign lymphoepithelial disorders and 5 cases low grade MALT lymphoma. Histological sections were stained routinely with hematoxylin and eosin (H&E and special stains. Immunohistochemical study was performed by LSAB2 method, by using primary antibodies for CD20, CD3, Kappa and Lambda light chains and Cytokeratin (Dako Denmark). **Results.** The 27 patients with Sjögren's sialoadenitis (22 women and 5 men), and 5 patients with MALT lymphoma (only women) were included in this analysis. According to the Ann Harbor Classification, all patients with MALT lymphoma had stage IE. Both groups of patients had an indolent clinical course, except permanent, rapid parotid enlargement in the patients with MALT lymphoma. Histologically, the periductal lymphoid infiltrate, gradually extended to the acini, completely replacing them by a sea of polyclonal lymphocytes, immunoblasts, germinal centers and plasma cells (confirmed immunohistochemically), but sparing the ducts and preserving lobular appearance. The histological feature of salivary gland MALT lymphoma included heterogeneous B-cell infiltrate that totally or subtotally had effaced the normal glandular structure. Malign lymphoepithelial lesions, representing infiltration of the ductal and epithelial structures by monoclonal neoplastic B-cells, positive for CD20, were highlighted by antibody to cytokeratin. **Conclusion.** The optimal diagnosis of salivary gland MALT lymphoma requires careful integration of clinical, morphological and immunohistochemical results.

Key words:
sjögren's syndrome; lymphoma, B-cell, marginal zone; diagnosis, differential; histology; immunohistochemistry.

Apstrakt

Uvod/Cilj. Sjegrenov sindrom je hronična autoimuna sistemska bolest okarakterisana poliglandularnom tkivnom destrukcijom, suvim keratitisom i suvim ustima. Ovi bolesnici imaju 44 puta veći rizik od razvoja limfoma, pri čemu je kod 80% njih prisutan MALT tip. Zbog nejasnih kriterijuma za razlikovanje benignih limfoepitelnih lezija pljuvačnih žlezda od MALT limfoma, cilj ove analize bio je obezbeđivanje praktičnih, kliničkih, histopatoloških i imunohistohemijskih informacija o njima. **Metode.** Od 32 parotidektomije, kod 27 nađen je Sjegrenov sijaloadenitis, a kod 5 MALT limfom. Laboratorijski preseci debljine 4 μm bojeni su hematoksilin/eozin (HE), Van Gieson, AB-PAS i LSAB2 metodama, uz korišćenje antitela na: CD3, CD20, kappa i lambda lake lance i panCytokeratin antigene. **Rezultati.** Analizom je bilo obuhvaćeno 27 bolesnika (22 žene i 5 muškaraca) sa Sjegrenovim sijalodenitisom i pet bolesnika (samo žene) sa MALT limfomom. U skladu sa *Ann Harbor* klasifikacijom svi bolesnici sa MALT limfomom bili su u stadijumu IE. Obe grupe bolesnika imale su blagi klinički tok, sem bržeg povećanja jedne parotidne žlezde kod onih sa limfomom. Za razliku od benignih limfoepitelnih lezija, MALT limfom odlikovao se difuznim i gustim monoklonskim B-ćelijskim infiltratom, uz brisanje normalne građe pljuvačne žlezde i malignim limfoepitelnim lezijama infiltrovanim monoklonskim tipom B limfocita potpuno ili delimično. Maligne limfoepitelne lezije, prikazane kao infiltracije duktusnih i epitelnih struktura monoklonskim neoplastičnim B-ćelijama pozitivnim na CD 20, prikazale su se pomoću antitela na citokeratin. **Zaključak.** Za optimalnu dijagnozu MALT limfoma pljuvačne žlezde neophodni su klinički, morfološki i imunohistohemijski nalazi.

Ključne reči:
sjegrenov sindrom; limfom, malt; dijagnoza, diferencijalna; histologija; imunohistohemija.

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Introduction

Sjögren's syndrome (SS) was named after the Swedish ophthalmologist Henrik Sjögren who presented his doctoral thesis in 1933 [1]. More recently, a number of studies have presented ground-breaking reports on SS, which now can be considered as a classical finding [2]. Sjögren's syndrome is a chronic autoimmune systemic disease characterized by polyglandular tissue destruction leading to keratoconjunctivitis sicca (KCS) and xerostomia [3–10]. Sjögren's syndrome is a worldwide disease and may occur in all ages. However, the peak incidence is in the fourth and fifth decades of life with a female/male ratio 9:1. It may develop alone (primary), or in association with an autoimmune diseases (secondary), the most frequent being rheumatoid arthritis and systemic lupus erythematosus [3, 8, 10]. Clinical course of SS is a slowly progressing disease, without rapid deterioration in salivary function, with systemic markers of disease activity, or dramatic changes in symptoms [3, 7, 8]. These patients have a 44-fold increased risk of developing salivary gland lymphoma, of which 80% are low-grade B cell lymphomas of mucosa-associated lymphoid tissue (MALT) [6]. The criteria for distinguishing benign lymphoepithelial lesions from MALT lymphoma in salivary glands are obscure and controversial [5, 11–18]. There are few studies on the natural course of primary SS, but it has been described as a stepwise, gradual progression from a disorder mainly in exocrine glands, to systemic extraglandular features and finally to lymphoid neoplasia development [2]. In general, primary SS is characterized by a stable and rather mild course of glandular or extraglandular manifestations, in contrast to the increased risk for development of malignant lymphoma [2]. But, in the study on survivorship in a population-based cohort followed from l976 to l992, the authors did not demonstrate an increased mortality of patients with primary SS [16]. Having in mind that the distinction between sialoadenitis usually in association with SS and early MALT lymphoma has difficulty proved using clinical criteria alone, we have decided to study the clinical, histopathological and immunohistochemical features of these diseases of the parotid gland.

Methods

Among 32 patients with parotidectomies, induced by Sjögren's sialoadenitis, sialoadenitis calculosis chronica or parotid gland tumors, 27 cases were identified as primary SS with benign lymphoepithelial disorder and 5 cases with MALT lymphoma. These cases spanned the period 2003 through 2007 years. The resected tissue specimens were fixed in 10% buffered formalin and embedded in paraffin. Paraffin tissue sections were cut at 5 μm and stained routinely with hematoxylin and eosine (H&E). The special stains used included periodic acid-Schiff (PAS), Giemsa and silver impregnation for reticulin. Immunohistochemical study was performed by using labeled streptavidin-biotin (LSAB) Kit (DAKO Denmark). Hematoxylin was used for counterstaining. The sites of peroxidase were visualized with diaminobensidine tetrachloride. Pretreatment (antigen retrieval) was performed by heating tissue sections in 800W microwave oven for 15 minutes with 0.1 mol/L citrate pH=6. Following primary monoclonal antibodies were used: pan-Cytokeratin (epithelial marker), CD20 (B-lymphocyte marker), CD3 (T-lymphocyte marker) and light chains of kappa and lambda (marker for polyclonal lymphocytes). Endogenous peroxidase activity was blocked with 3% hydrogen peroxide solution. Nonspecific binding was reduced with 10% normal goat serum block before incubation. Appropriate positive and negative controls were included.

Results

Of 32 patients with parotidectomies, Sjögren's sialoadenitis was discovered in 27 patients (22 women and 5 men) and MALT lymphoma in 5 women. The median age at the time of parotidectomy was 52 years for patients with Sjögren's sialoadenitis and 59 years for patients with MALT lymphoma. The duration of sicca symptoms (keratokonjunctivitis sicca and xerostomia) was from 4.7 to 9.5 years for Sjögren's sialoadenitis and, about six years before the diagnosis for MALT lymphoma. The patients were typically presented with a painless mass that showed episodic enlargement. Two of the patients had a facial nerve paresis and pain. The important clinical sign of MALT lymphoma was permanent, rapid enlarged of parotid gland.

Histologically, periductal and perivascular dense round cell infiltrate extended to the acini and formed lymphoid follicles, often with germinal centers (Figure 1). Somewhere,

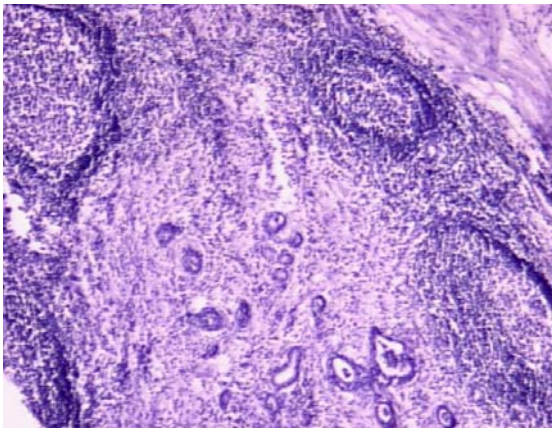

Fig. 1 – Marked acinar atrophy, mononuclear infiltrate and lymphatic follicles with germinal centers (HE ×200)

the parotid glands were completely replaced by a sea of polyclonal lymphocytes, plasma cells and macrophages. The stroma of the gland was preserved, an appearance that helps to differentiate this disorder from a lymphoma. Slightly dilated ducts without acini, the important characteristic of glandular atrophy, were seen everywhere (Figure 2). The characteristics of the late stage in the course of Sjögren's' sialoadenitis were also seen, predominantly atrophy of the acini, fibrosis (Figure 3), hyalinization, fatty infiltration and nests of oncocytic cell degeneration (Figure 4). Proliferating lymphoepithelial cells surrounded remnants of the damaged ducts, forming so-called benign lymphoepithelial islands.

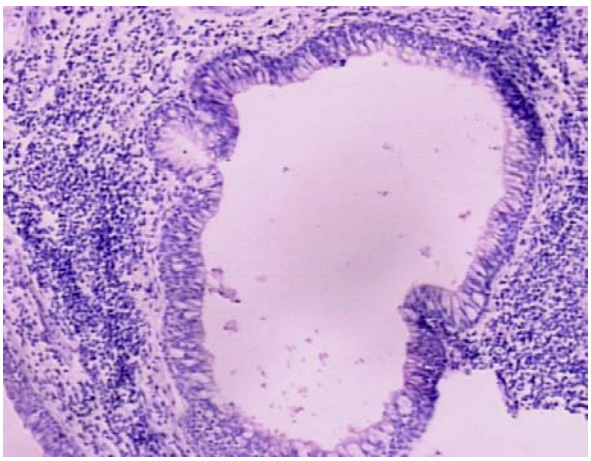

Fig. 2 – Periductal lymphocytic infiltrate with sialoduct ectasia (HE ×200)

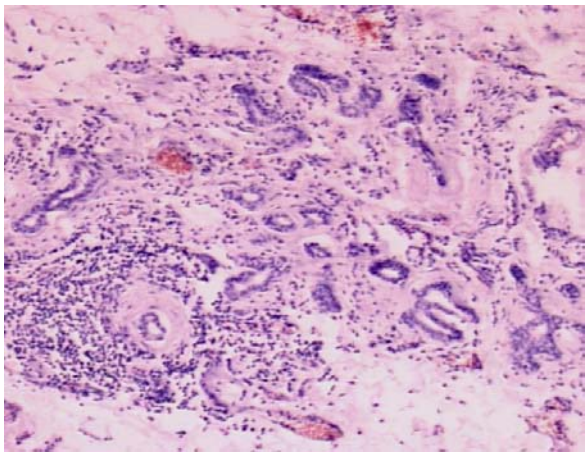

Fig. 3 – Atrophic glands replaced by lymphoid infiltrate, lymphatic follicles and wide stromal fibrosis (HE ×200)

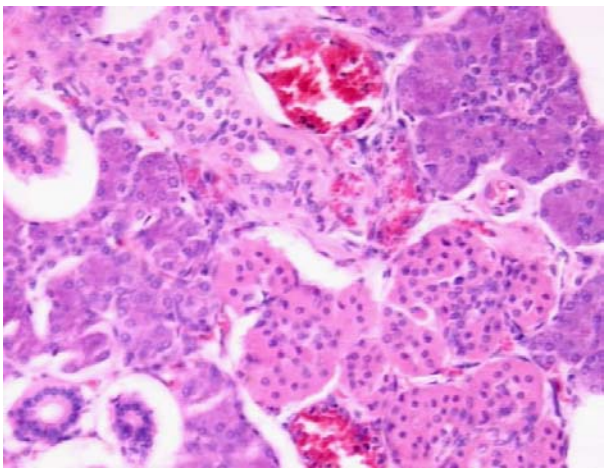

Fig. 4 – Oncocytic adenomatoid metaplasia in the atrophic parotid gland tissue (HE ×400)

Immunophenotypic analysis, performed on paraffin sections, demonstrated that the majority of inflammatory cells were of polyclonal type.

The parotid gland was diffusely and extensively infiltrated by neoplastic lymphoid cells that disintegrated it, leaving only the clusters of degenerative cells and residual ducts among the lymphoid infiltrate (Figure 5). The lymphoma cells showed varied cytological appearances, often with individual specimens. The most numerous cells of salivary MALT lymphoma had small to medium-sized, slightly irregular nuclei with moderately dispersed chromatin and inconspicuous nucleoli, resembling those of centrocytes; they had relatively abundant, pale cytoplasm. With the accumulation of more palecytoplasm, and distinct cell borders, neoplastic cells had the monocytoid appearance (Figure 6), or

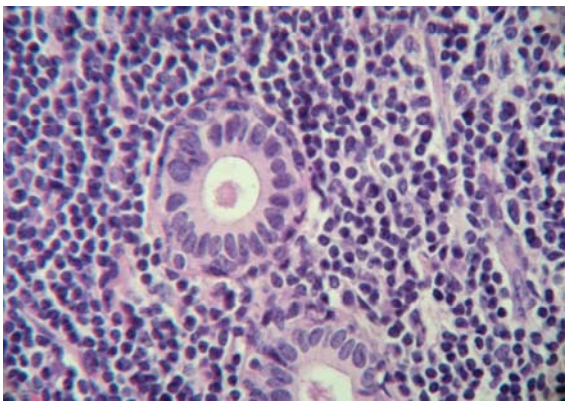

Fig. 5 – Salivary gland is replaced by a dense and extensive lymphocytic infiltrate with residual two ducts (HE ×400)

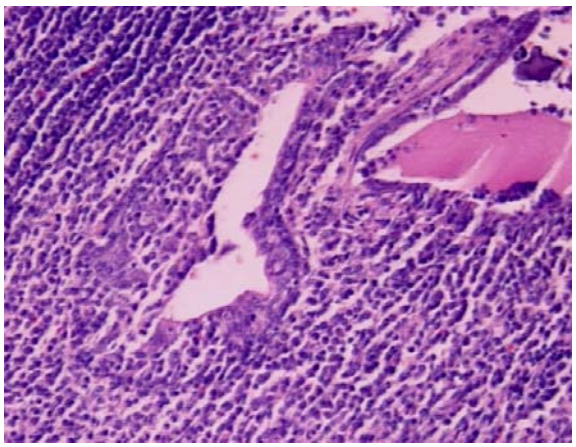

Fig. 6 – Lymphoepithelial lesion with numerous pale lymphoid cells. These centrocyte-like/monocytoid appearing cells extended beyond them, forming the confluent sheets (HE ×200)

resembled small mature lymphocytes. Somewhere, variable numbers of plasma cells were frequently present, often adjacent to the epithelium. Scattered large transformed centroblast- or immunoblast-like cells were usually dispersed throughout the lymphoma. The immunophenotype of the neoplastic cells of MALT lymphoma was CD20 +, highlighting the extensive B-cell infiltrate, particularly around ducts (Figure 7). An important diagnostic feature of MALT lymphoma at many sites was the presence of malign (lymphoepithelial lesion (LEL) defined by the infiltration and destruction of the epithelial structures, often together with eosinophilic degeneration, by aggregates of neoplastic lymphoid cells and lymphoid follicles, highlighted by panCytokeratin and by CD20 (Figures 8 and 9).

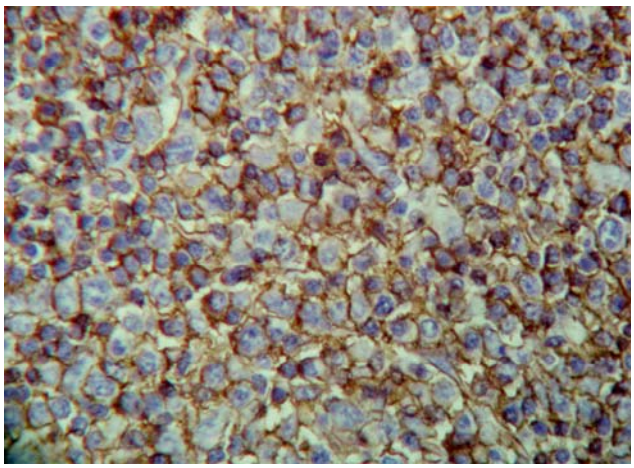

Fig. 7 – Immunophenotypic staining demonstrated that the majority of cells are CD20+ (LSAB ×400)

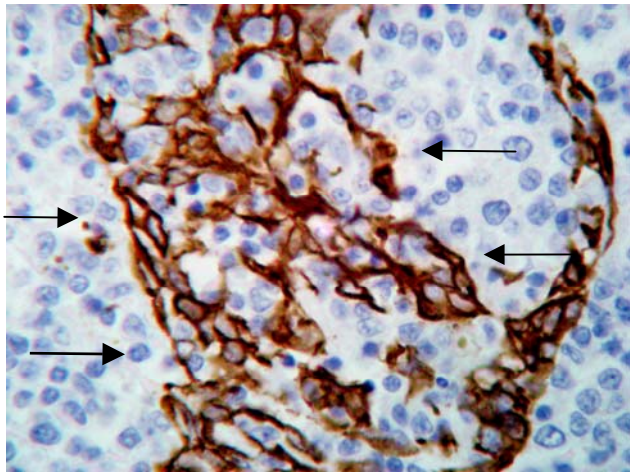

Fig. 8 – Lymphoepithelial lesions – positive expression of panCytoceratin inside ductal epithelium and negative inside infiltrative lymphocyte cell field (LSAB ×400)

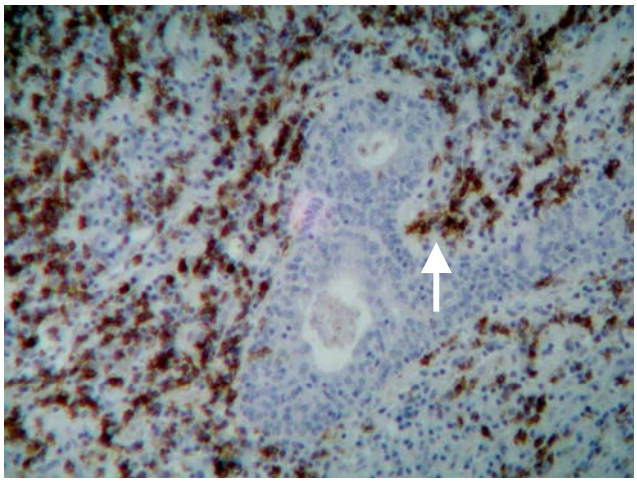

Fig. 9 – Lymphoepithelial lesions – positive expression of CD20 inside ductal epithelium, infiltrated by lymphocytes (LSAB ×400)

The tumor cells of MALT lymphoma expressed the marginal zone cell-associated antigens (CD20), immunoglobulin light chain restriction and the lack of CD3 antigen, not only in lymphocytes adjacent to the lymphoepithelial lesions, but also within the lymphoepithelial lesions (Figures 9).

Discussion

There are clinical evidences that SS and lymphoma are linked. The risk of B cell non-Hodgkin lymphoma (NHL) is by 44 times greater in patients with SS than in healthy population affecting about 5 percent of patients with SS [2, 6, 13–16, 19–25]. There are few studies on the natural course of primary SS, but it has been described as a stepwise, gradual progression of lymphoid disorder mainly in exocrine glands, to systemic extraglandular features and finally to lymphoid neoplasia development [2, 26]. However, in general primary SS is characterized by a stable and rather mild course of glandular or extraglandular manifestations, in contrast to the increased risk for development of malignant lymphoma [2, 25–30]. In a study on survivorship, in a population-based cohort followed from 1976 to 1992, the authors did not demonstrate increased mortality of patients with primary SS [18]. The salivary gland lymphoid infiltrates, associated with LEL, include broad spectrum of lympho (plasmocytic) proliferations that range from benign to small B cell lymphomas to large B- ell lymphomas [12, 28–33]. Depending on the precise type of proliferation, they go by a variety of different terms: benign lymphoepithelial (myoepithelial), sialoadenitis/extranodal marginal zone B cell lymphomas (MZL) or MALT type / high grade MALT lymphoma (diffuse large B cell lymphoma) [26–30]. About half of the cases are associated with SS or another autoimmune disorder such as rheumatoid arthritis, that was also confirmed by us in one case [25, 30]. Whereas most lesions with LEL in the past were considered benign but the categorization of these lesions now has become confusing due to varying criteria for lymphoma and recognition by some of borderline lesions or a "clonal disorder of uncertain malignant potential" [25–28].

SS presents with a wide variety of clinical features. Onset of the disease is insidious and patients have difficulty in determing when the disease actually started. Keratoconjunctivitis sicca and xerostomia (so-called sicca complex) are the main clinical presentations in adults, whereas bilateral parotid swelling can be an obvious sign at juvenile disease onset [2]. More than half of the patients may develop the extraglandular manifestations during the evolution of the disease. Occasionally, systemic features may lead to the diagnosis [2, 25, 30].

Anti-inflammatory therapy in primary SS significantly improved subjective symptoms and objective ocular signs [2, 8, 22, 33–37]. Artificial tears and soft contact lenses often alleviate the patient's ocular complains, and are of importance in preventing corneal damage and conjunctivitis [2, 37]. However, we did not find evidence that anti-inflammatory treatment increases tear production in these patients.

The management of dry mouth aims to prevent and treat infections, periodontal disease and dental caries. To reduce the risk of caries, it is necessary to maintain a good oral hy-

giene. Artificial saliva products and special toothpaste may also be benefit for certain patients, and fluoride supplementation is advocated. Eradication of oral candidiasis usually provides significant improvement of oral symptoms [2, 26]. Oral pilocarpine has been shown to be a safe treatment and provide significant subjective and objective benefits for patients suffering from symptoms associated with xerostomia. Another therapy includes systemic use of interferon-alpha, which may be of benefit for the symptoms associated with xerostomia.

The optimal therapeutic strategy for salivary MALT lymphoma is not yet defined and depends on the clinical stage of removed MALT lymphoma [2, 12, 15, 33]. On the basis of some retrospective analysis, the authors have concluded that there is no significant difference in outcomes among patients undergoing a variety of treatment modalities (surgery, radiotherapy, chemotherapy) and those undergoing to long-term follow-up [2, 12, 15, 26, 28, 33–37].

Among the possible etiologic and triggering factors involved in Sjögren's syndrome, the discussion on relationship between viral infections causing the development of autoimmune reactions, began some decades ago [3, 12, 23, 24]. The putative role of different viruses can be viewed in the light that salivary glands are a site of latent viral infections and that lymphotropic viruses have the potential to trigger the autoimmune process. Some of the immunoreactive regions within the La/SS–B protein have been found to have sequence similarities with proteins of Epstein-Barr virus (EBV) and HIV-1. It seems reasonable that these viruses can promote autoantibody production [3, 24, 26, 30].

Immunohistological analysis of lymphoid cell infiltration in the exocrine glands in SS shows a predominance of T-cells with fewer B-cells and macrophages [3, 23, 24]. The majority of T-cells in the lymphocytic infiltrates are CD4+ T-helper cells with CD4/CD8 ratio well over two. Most of these T-cells bear the memory phenotype and may contribute significantly to B cell hyperactivity. The B-cells make up roughly 20% of the infiltrating cell population in the affected glands, producing immunoglobulins with autoantibody activity. About 75% of patients have rheumatoid factor regardless of whether coexisting rheumatoid arthritis is present or not [26, 30–36]. Rheumatoid factor is also commonly found in saliva, tears and the circulation. Antinuclear antibodies (ANAs) are detected in 50–80% of patients and a positive LE test result is present in 25% [35]. Most important, however, are antibodies directed against two RNP antigens, SSA (Ro) and SSB(La) which can be detected in up to 90% of patients [2, 35]. Those with high titers of antibodies to SSA are more likely to have extraglandular manifestations, such as cutaneous vasculitis and CNS disease [35]. The finding of serum autoantibodies directed against the muscarinic M3 receptor (expressed in salivary and lacrimal glands) in the majority of patients is an important advance in understanding the pathogenesis of impaired glandular function in SS [2]. Oligoclonal or monoclonal B cell expansion, arising mainly from salivary glands but also from visceral organs and lymph nodes, has been reported to occur in 14–100% of SS patients [18–23]. In this respect, SS appears to be a crossroad between autoimmunity and malignancy and it is suggested that patients with evidence of clonal expansions of B-cells in their salivary glands are at high risk of developing malignant lymphoma [2, 26, 30–36]. Sjögren's syndrome represents a pathological model of the evolution from polyclonal B lymphocyte activation to oligoclonal/monoclonal B-cell expansion, which may culminate in the development of a malignant lymphoproliferative disease [33–35]. Different phases of this process are usually marked by the appearance of antigen-driven activated B-cell clones, which are commonly IgM-positive and with rheumatoid factor (RF) activity. However, the antigen able to trigger B-cell proliferation is still unknown. Immunoglobuline products of the neoplastic B cells were RF. Contrary to the expectations, they did not react with nuclear or cytoplasmic antigens, double-stranded DNA, self antigens commonly bound by natural autoantibodies, or SG tissue [33–36].

The reported data on genetic abnormalities such as numerical chromosomal aberrations, translocations, mutations and inactivation of the tumor suppressor genes, p53 and p16 in salivary MALT lymphoma are contradictory [2, 21, 33–35].

An optimal therapeutic strategy for salivary MALT lymphoma has not yet been defined and depends on the clinical stage of a removed MALT lymphoma [2, 12, 15, 33]. On the basis of some retrospective analysis, the authors have concluded that there is no a significant difference in outcomes among patients undergoing a variety of treatment modalities (surgery, radiotherapy, chemotherapy) and those undergoing a long-term follow-up [2, 12, 15, 26, 28, 33–37].

Conclusion

Based on the results of this study we consider that an optimal diagnosis of MALT lymphoma requires a careful integration of the following clinical, histopathological and immunohistochemical findings: rapid and persistent enlargement of the parotid gland, destruction of lobular parotid gland structure by extensive and dense lymphoid infiltrate, presence of monoclonal B-cell infiltrate and presence of malign lymphoepithelial lesions.

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