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RELATO DE CASO

Mucosa-associated lymphoid tissue lymphoma in labial minor salivary glands - case report and literature review

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Abstract:

Mucosa-associated lymphatic tissue (MALT) lymphomas commonly occur in the stomach however, rare cases of MALT lymphomas involve the minor salivary gland. We did a literature review and described the fourth case in the English literature of adults affected by a MALT lymphoma in the lip. A 68-year-old woman with probable primary Sjögren's syndrome (SS) was referred to our dentistry and stomatology service, complaining that her lower lip had progressively thickened during the past 4 years. An incisional biopsy was performed, and the microscopic examination showed a dense, diffuse lymphoplasmacytic infiltration of the salivary glands, with plasmacytic differentiation. The immunohistochemical analysis revealed diffuse positivity of the neoplastic cells for CD20 and BCL-2; the plasma cells were positive for CD138 and Lambda, which was consistent with MALT lymphoma. SS and Immunoglobulin G4-related disease were excluded. The total regression of the lesion was obtained after treatment with surgery, chemotherapy, and radiotherapy.

Keywords: Minor Salivary Glands; Marginal Lymphoma B-Cell; Treatment Outcome

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INTRODUCTION

Mucosa-associated lymphatic tissue (MALT) lymphomas is the most common extranodal non-Hodgkin's lymphoma.[1] Isaacson and Wrigh[2] reported in 1983 the first case, and the most commonly affected and best-studied site is the stomach.[1] Cases of primary salivary gland lymphomas are rare, constituting less than 5% of non-Hodgkin's lymphoma cases in adults.[3]

Disorders causing immunosuppression such as, human immunodeficiency virus (HIV) infection, autoimmune diseases (celiac disease, Crohn's disease, Sjögren's syndrome [SS], and Hashimoto's thyroiditis), *Helicobacter pylori* infection and chronic inflammatory stimulus (eg, habitual lip chewing, chronic gastritis) are described as risk factors for the development of MALT lymphoma.[4–7]

MALT lymphomas are more prevalent in females over 60 years.[6] Nevertheless the epidemiology of MALT lymphomas in the lips appear to be different, showing a predilection for young people. The literature describes a few cases of MALT lymphomas involving the minor salivary gland, we reported the fourth case in the English literature of MALT lymphoma in the lips of adults and did a literature review pointing out the risk factors and methods of treatment.

CASE REPORT

A 68-year-old woman was referred to our Dentistry and Stomatology Service in 2014, complaining of lip thickening during the past 4 years. She had a positive medical history of arthrosis, probable diagnosis of primary SS and chronic gastritis with confirmed *H. pylori* presence. She brought some slides from previous biopsies consistent with chronic sialadenitis for review. An extraoral examination revealed left lower lip with significant enlargement to the left (Figure 1). Intraoral examination showed diffuse swollen with fibrous aspect at palpation.

Formerly, she was diagnosed with probable primary SS due to 2 subjective and 1 objective criteria. She complained of dry mouth and dry eyes with an unstimulated salivary flow rate < 1.5 mL in 15 minutes, however salivary glands scintigraphy was normal. Ocular objective signs (Schirmer's test) was normal as well. Later, serological exams showed absence of serum antibodies (Anti-Ro/SSA, Anti-La/SSB, anti-nuclear factor, and rheumatoid factor). Review of previous slides confirmed the presence of intense plasma cells infiltrate around the salivary glands parenchyma.

Another incisional biopsy was performed in our service, and the microscopic examination showed a dense, diffuse lymphoplasmacytic infiltration of the salivary glands, with partial plasmocytic differentiation. An immunohistochemical analysis revealed diffuse positivity of neoplastic cells for CD20 and BCL-2 as well as negativity for CD5, CD23, CD10, and cyclin D1. Areas with plasma cell differentiation were positive for CD138 and lambda and negative for kappa, which is consistent with extranodal marginal-zone lymphomas of the MALT type (Figure 2). After immunohistochemistry staining for immunoglobulin G4 was negative excluding IgG4-related disease. These histopathological findings such as a pre-existing lymphoma excluded SS in Vitali criteria.[7]

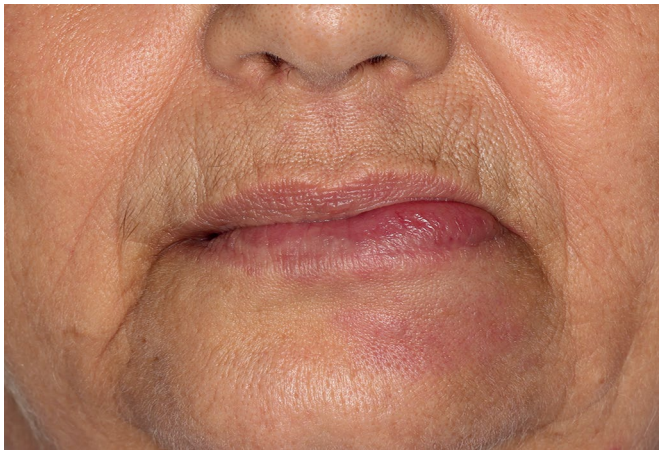

Figure 1. Initial clinical image showing enlargement on left inferior lip and mild erythema on chin.

Surgery was the first treatment proposed, however, complete removal was not possible in this topography. After patient underwent six cycles of targeted therapy with rituximab. Due to poor response, it was followed by radiotherapy, which resulted in complete regression of lesion. Radiotherapy was the last option of treatment to avoid dry mouth severity in the first moment. She received a total dose of 36 Gy divided into 24 sessions. She remains disease free 3 years after treatment (Figure 3).

DISCUSSION

MALT lymphomas involving salivary glands are mainly localized in the parotid gland, rare cases are in the minor salivary glands.[8] The rarity of the reported cases of this type of MALT lymphoma in the literature contributes to the dismissal of the diagnosis with other comorbidities such as mucocele, irritation fibroma and mesenchymal tumors in lip topography, which raise doubts regarding the best method of treatment.[6,9,10] in the English literature described 22 cases of MALT

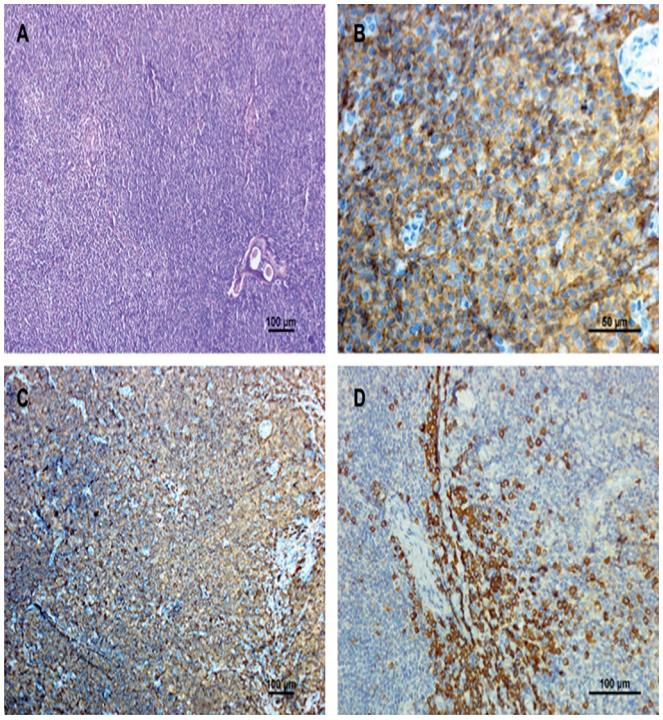

Figure 2. A - Photomicrography stained with hematoxylin and eosin showing diffuse lymphoplasmocytic infiltrate, consisting of small lymphocytes, with scarce cytoplasms and hyperchromatic nuclei, with relatively dense chromatin (x100); B and C - Photomicrography evidencing strong positivity in immunostaining for CD20 (x200); D - Strong positivity for lambda light chain (x200).

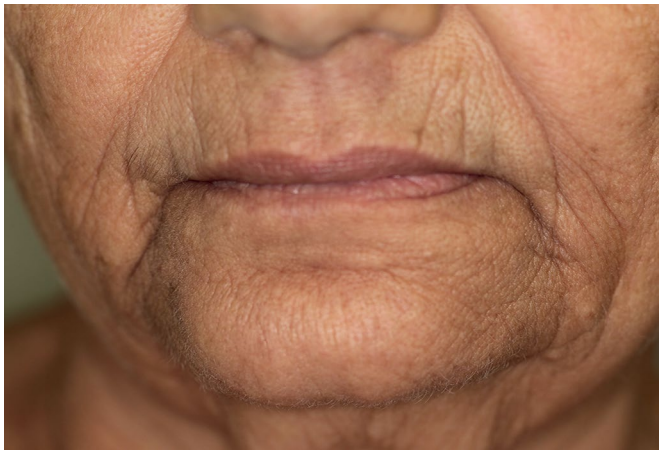

Figure 3. Final clinical image showing the complete regression of enlargement in left inferior lip.

lymphomas in the minor salivary gland. Of this small sample, the lip was a primary site in 6 cases, and three cases were not associated with autoimmune disorders. The patients' ages ranged from 7 to 83 years (mean age 40), and females had a 2 times higher incidence rate than males.

Studies[14] have suggested that nongastric MALT lymphomas are associated with autoimmune disorders (eg, Hashimoto's thyroiditis, SS, Crohn's disease) and infectious agents (eg, *H. pylori*, *Chlamydophilapsittaci*, *Campylobacter jejuni*, *hepatitis C*, *Borrelia burgdorferi*). Moreover, chronic inflammatory stimulus due to persistent inflammation or infection increases the lymphoid population—primarily the T lymphocytes, which might suffer genomic changes and become neoplastic.[7,12,13]

Twelve cases of primary labial MALT lymphomas were found in English literature in children and adult patients (Table 1). Surprisingly, some of our findings contradicted the literature. The literature shows that patients tend to be females over 60 years old; however, in our review, the patient's ages ranged from 7 to 60 years old (mean age = 22 years old) and the lymphomas showed no sex predilection (6:6). In these studies, 3 cases were associated with autoimmune diseases (25%), 4 were associated with an *H. pylori* infection (33%), 2 were associated with lip chewing (16%), and 5 did not find associated factors (42%). Though there is an association between autoimmune disorders, infectious agents and chronic inflammatory stimulus, this link is not well established yet. 42% of the patients in the review were healthy, young and had no clear associated factor to develop MALT lymphoma in the lip.[5,7,8,10,11]

Nevertheless, *H. pylori* infection appears to be the most important risk factor since is common among all ages. Lip chewing was a factor found only in children, and autoimmune disease in adults over 33 years old (mean age of 51 years old). These findings also suggest that MALT lymphomas in the lip can have a particular epidemiology and etiology according to age. When we analyze the sample between adults and children we have 8 children under 14 years old (57% of total), mean age of 10 years old, male preference (5:3) and half of them didn't show any risk factor.

On the other hand, the adult sample is composed mainly of women (3:1), mean age of 45 years old and there's a clear association between risk factors and MALT lymphoma in the lip. All adult women suffered from autoimmune disorder and two had also *H. pylori* infection. Our patient was the oldest of the sample (68 years old), with positive *H. pylori* infection and autoimmune disease, supporting this association.

The relation between *H. pylori* and gastric MALT lymphomas has been well established.[5,6,12] The total remission of 60% to 80% of gastric MALT lymphomas

Table 1. Case reports of primary MALT lymphomas in the lip and present case

Case	*Sex*	*Age*	*Treatment*	*Remarks*	*Outcome*	*Year*	*Reference*
1	F	60	CT+ RT (parotid) + S (residual lesion of the Lip)	SS, It was not tested H. pylori infection. Lip + Parotid	12 mo DF	1998	Odell et al.[23]
2	M	10	ATB	H. pylori infection	12 mo DF	1998	Berrebi et al.[24]
3	M	12	CT	WRF	12 mo DF	2004	Mo et al.[6]
4	M	14	S	WRF	WD	2006	Zambrano et al.[16]
5	F	33	ATB + CT	H. pylori infection, SS, Hashimoto's thyroiditis	36 mo DF	2009	Niscola et al.[25]
6	F	7	S + CT	Lip biting and physical stimuli	6 mo DF	2009	Ryu et al.[11]
7	F	9	S + CT	WRF	24 mo DF	2011	Crandley et al.[8]
8	M	11	S	Lip biting	36 mo DF	2011	Bombeccari et al.[7]
9	M	11	S	WRF	12 mo DF	2013	Gabali et al.[12]
10	F	60	ATB	H. pylori infection, SS, Chronic candidiasis	72 mo DF	2013	Keszler et al.[26]
11	M	27	S	WRF	29 mo DF	2014	Kawasaki et al.[13]
12	F	9	ATB + Prednisone	H. pylori infection	6 mo DF	2015	Sedrak et al.[27w]
13	F	68	S + CT + RT	H. pylori infection + Arthrosis	36 mo DF	2018	Present Case

CT, Chemotherapy; *RT*, Radiation therapy; *S*, Surgery; ATB, Antibiotic therapy; WRF, Without risk factor DF, months disease free.

can be acquired after the exclusive eradication of *H. pylori* with antibiotics.[14,15] On the other hand, the use of antibiotic therapy in nongastric MALT lymphomas remains controversial,[16–18] regardless of reports showing total remission of MALT lymphomas in the salivary gland after exclusive *H. pylori* treatment.[5,13]

In regard to treatment, the protocols are heterogeneous. Treatment options include antibiotic treatment, surgery, radiotherapy, chemotherapy with or without immunotherapy, and even a "wait-and-watch" policy.[16] For localized MALT lymphomas, surgical excision is indispensable for diagnosis. In some sites, it can be the initial option for treatment and it can be followed by locoregional radiotherapy, locoregional chemotherapy, or immunochemotherapy when the margins of the specimen are compromised by the tumor.[19] However, radiotherapy is the preferred therapy.[20]

Because of the characteristic latency of MALT lymphomas, a watch-and-wait strategy can be adopted in cases with localized disease.[15,21] Mainly in cases of elderly patients who require extensive irradiation, it can be used to spare the patients from the side effects of the therapy.[1] When using this approach, it is important to perform periodic local and systemic evaluations for a long period of time because it may take years for the disease to progress.[22]

CONCLUSION

In conclusion, the review of the literature suggests that MALT lymphomas in the lip can have a particular epidemiology and etiology according to age. The development of MALT lymphoma in adults has a stronger association with risk factors such as autoimmune disorder and *H. pylori* infection. There are still a few cases in the literature to confirm such hypothesis and fully understand the etiology and epidemiology of MALT lymphoma in the lips, but with this review was possible to formulate an initial study.

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