Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue-type in the lower labial minor salivary gland of a patient with Sjögren's syndrome

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Abstract: Patients with autoimmune and chronic inflammatory conditions are at increased risk of developing lymphoma. We report a case of extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) in a 60-year-old woman who has been treated for Sjögren's syndrome for the last 8 years. She was referred to our hospital because of a painless swelling in her left lower lip. There were no clinical signs of major salivary gland swelling or systemic lymphadenopathy. The tumor was removed surgically, and microscopic examination showed it to be characterized by lymphoepithelial lesions, proliferation of centrocyte-like cells, and follicular colonization, leading to the diagnosis of MALT lymphoma. The patient has undergone periodic systemic examination without evidence of tumor recurrence for 18 months since the surgical treatment. The present report supports the postulation that the labial salivary gland biopsy can offer early diagnostic clues to lymphoma development in patients with underlying Sjögren's syndrome.

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Key words: MALT lymphoma, labial salivary gland, Sjögren's syndrome

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Introduction

Mucosa-associated lymphoid tissue (MALT) lymphoma was first identified by Isaacson and Wright in 1983 (1) and is now established as a distinct subtype of non-Hodgkin's lymphoma (2). It was documented that the occurrence of MALT lymphoma is the major complication in the course of patients with Sjögren's syndrome and that patients with Sjögren's syndrome have a 16-fold (3) or up to 44-fold (4) increased risk of developing lymphoma compared with the general population. Most recently, Mello *et al* (5), with 3 cases of B cell MALT lymphoma diagnosed by labial minor salivary gland biopsy in patients screened for Sjögren's syndrome, emphasized the importance of histopathological confirmation of the affected salivary gland for the diagnosis of lymphoma development. In this report, we describe a case of MALT lymphoma in the lower lip of a patient in association with Sjögren's syndrome and benign lymphoepithelial lesions of minor salivary gland.

Case report

A 60-year-old Japanese woman with an 8-year history of

Sjögren's syndrome was referred to the Nippon Dental University Hospital because she had recently noticed the enlargement of a painless mass in her lower lip. The patient was asymptomatic except for dry mouth and had no history of pre-existing lymphoma or persistent major salivary gland swelling at the time of clinical diagnosis. On the basis of clinical signs that a nodule in her lip was demarcated and covered by intact mucosa without inflammatory symptoms, the tentative clinical diagnosis was benign salivary tumor of the labial gland. The patient underwent surgical excision of the lower lip mass.

The surgically-removed tissue specimen, 9.5×5.5×4.5 mm in mass, was presented for pathological examination. The cut surface was gray to white, and showed a homogenous appearance (Fig. 1a). The specimen was fixed in 20% buffered formalin and routinely processed for paraffin embedding. After routine microscopic examination of hematoxylin/eosin-stained sections, serial sections were used for immunohistochemical examination with a panel of antibodies, as listed in Table 1.

Histopathological examination showed that a nodular tumor mass accompanying residual salivary gland lobuli was demarcated by fibrous capsule (Figs. 1b & c). The main

Table 1. Panel of antibodies used in study.

antibody	clone	source	dilution and pretreatment
CD3	polyclonal	Dako	1:50, AC [§]
CD10	56C6	Novo Castra	1:200, AC
CD20	L26	Dako	1:400, AC
CD21	1F8	Dako	1:100, Pro [¶]
CD23	1B12	Novo Castra	1:20, AC
CD79a	JCB117	Dako	1:200, AC
bcl-2	124	Dako	1:40, AC
bcl-6	polyclonal	Dako	1:25, AC
CAM5.2	CAM5.2	Becton-Dickinson	1:5, Pro
kappa light chains	A8B5	Dako	ready-to-use, Pro
lambda light chains	N10/2	Dako	ready-to-use, Pro

[§]AC, autoclave; [¶]Pro, protease

lesion was featured by lymphoid follicles with the rim of a thin mantle zone and infiltration of lymphoid cells including both small and large atypical cells (Fig. 1d). Small lymphoid cells, larger in number, were characterized by their slightly folded nuclei with moderate- to high-density chromatin and inconspicuous nucleoli, whereas large cells with irregular nuclear contours were fewer (Fig. 1e). These lymphoid infiltrates comprised monotonous centrocyte-like (CCL) cells with monocytoid cells and plasma cells. Within the tumor mass, lymphoepithelial lesions were assigned by the inclusion of ductal and epithelial structures with lymphocyte infiltration (Fig. 1f). Immunohistochemistry proved that the CCL cells were positive for CD20 (Fig. 1g), bcl-2 (Fig. 1h), and CD79a (Fig. 1i) indicating B-cell phenotype, and negative for CD3, CD10, CD23 and bcl-6. A cluster of these immunophenotypic cell zones was segregated spatially from CD3-positive T cells (Fig. 1k), supporting the follicular colonization of lymphoma cells, although a variable number of CD3-positive T cells were admixed with CCL cells. Most of the proliferating tumor cells were also validated to be kappa-negative and lambda-negative cells, indicating a lack of light chain restriction (data not included). Immunostaining with CD21 helped to decipher a disrupted follicular dendritic cell pattern that is a critical diagnostic criterion of follicular colonization in MALT lymphoma (Fig. 1l). Regarding the lymphoepithelial lesions, the epithelial components were highlighted by CAM5.2 staining (Figs. 1m & 1n).

With the final pathologic diagnosis of MALT lymphoma, the patient was immediately referred to oncology for general examination and follow-up. Fortunately no systemic symp-

toms were detected at that time and the patient has continued to undergo periodical systemic examination without evidence of tumor recurrence and dissemination to distant sites for 18 months since the surgical treatment.

Discussion

MALT lymphomas are low-grade B-cell lymphomas and tend to remain localized for a prolonged period, although they can transform into high grade malignancies. Primary lymphomas of the salivary gland are rare, accounting for only 2.4-4.5% of salivary gland tumors with their preferential occurrence in parotid (50-93%) and submandibular glands (6, 7). From an etiological point of view, the most important finding has been the elevated occurrence of the tumor, 43% of patients in association with underlying Sjögren's syndrome (7). Table 2 gives a summary of lymphoma cases associated with Sjögren's syndrome on the basis of a survey of the literature since 2000 (8-25). The tumor occurred predominantly in adult patients aged over 50 years and with female predominance, which was consistent with the incidence of Sjögren's syndrome. Histopathologically, 23 of 27 cases (85%) were diagnosed as MALT lymphoma with 9 salivary malignancies, and a third of these cases had multiple lesions. Four cases (5) including the present case showed development of MALT lymphoma in the labial salivary gland (Table 3). All the cases in the labial salivary gland occurred in middle-aged women, and none of the patients appeared to have pre-existing lymphoma or persistent major salivary gland swelling at the time of evaluation.

Table 2. Summary of cases of malignant lymphoma in patients with Sjögren's syndrome

pathological diagnosis	cases	age (yrs)	sex	location	references
MALT lymphoma	23	28-88 [§]	M (1) [¶]	salivary glands 9	5, 8-10
			F (22)	thymus 6, stomach 3, lung 3 and others 12	9,11-21
splenic marginal zone lymphoma	1	67	F	spleen	22
diffuse large B cell lymphoma	2	60, 62	F (2)	tongue 1, cerebrum 1	23, 24
Hodgkin's lymphoma	1	40	F	liver and bone marrow	25

[§]mean $\pm$ SD = 50 $\pm$ 13.8; [¶]parenthesis indicates the number of cases

Fig. 1. MALT lymphoma in the labial salivary gland of a patient with Sjögren's syndrome. (a) Gross finding of surgical specimen. Bar = 5 mm. (b-f) Histological findings, hematoxylin/eosin (HE) stain. Immunostaining for CD20 (g), bcl-2 (h), CD79a (i; j, high power view), CD3 (k), CD21 (l), and CAM5.2 (m; n, high power view), immunoperoxidase stain, hematoxylin counterstain. (b) $\times 10$, (c) $\times 100$, (d, g-i, k-m) $\times 40$, (e-f, j, n) $\times 400$.

The cut surface of the surgical specimen showed whitish solid appearance. The tumor mass was circumscribed with fibrous capsule (a). Microscopically, residual salivary gland tissue was found at the peripheral region of tumor mass indicated by rectangle c in panel b (c). Proliferation of lymphoid cells with lymphoid follicles and a thin mantle zone were observed in rectangle d in panel b (d). There were follicular colonization of centrocyte-like (CCL) cells (e) and lymphoepithelial lesions (f). Immunohistochemically, most of the CCL cells showed positive reactions for CD20 (g) and CD79a (i, j), and many of them were positive for bcl-2. These immunophenotypic cell zones were segregated spatially from CD3-positive T cells, although a variable number of CD3-positive T cells were admixed with CCL cells (k). CD21 positive follicular dendritic cells were disrupted in the periphery of the tumor (l). Epithelial components were highlighted by CAM5.2 (m, n).

Table 3. MALT lymphoma of the minor salivary glands.

case	age (yrs)	sex	location	duration of Sjögren's syndrome treatment (yrs)	references
1	55	F	labial gland	25	5
2	53	F	labial gland	2.5	5
3	51	F	labial gland	3	5
4	70	F	palatal gland	13	8
5	60	F	labial gland	8	present case

To date, it is inferred that the increased lymphoma risk in patients with underlying Sjögren's syndrome or other autoimmune diseases is mainly due to high inflammatory activity and severity of disease, rather than disease-associated treatment. Accumulation of genetic abnormalities including bcl-2 over-expression as we confirmed in the present case, may be important for tumor cells to evade apoptosis in the progression from local lymphoid hyperplasia to neoplastic transformation under chronic stimulation at the site of the autoimmune reaction. It is recommended that both clinicians and pathologists should be aware of the potential risk for lymphoma development through latent and progressive stages in patients with features of Sjögren's syndrome and, on suspicion of tumor development, clinicians should provide examination and follow-up in order to determine the extent of the disease and search for evidence of progression and dissemination to extraglandular sites.

In this report, we have described a case of MALT lymphoma in the labial minor salivary gland of a patient undergoing 8-years of treatment for Sjögren's syndrome. Although preoperative diagnosis of salivary malignant lymphoma should be considered for patients with Sjögren's syndrome, in the present case it was not feasible to make a differential diagnosis based on the clinical diagnosis alone. Mello *et al* (5) emphasized that by performing labial salivary gland biopsies, particularly from patients with Sjögren's syndrome, clinicians can find lymphomas which might otherwise escape detection. Microscopic examination of the tumor in the present case, showing morphologic features of CCL cells, plasmacytoid cells, and lymphoepithelial lesions as well as their immunophenotypes, was helpful for reaching a definitive diagnosis. In relation to the postulated progressive nature of lymphoma development under chronic autoimmune reactions, much attention has been given to light chain restriction because the presence of a monoclonal population of B cells may provide prognostic information as to lymphoma development with plasmacytotic differentiation. In the present case, most of the tumor cells remained negative for both immunoglobulin light chains, suggesting that the tumor might have been at a premature stage prior to massive monoclonal B-cell proliferation.

In conclusion, the present experience underscores the need for awareness of the possibility that lymphoma development may occasionally involve minor salivary glands without any apparent signs of major salivary gland involvement in patients with underlying Sjögren's syndrome. Early detection of lymphoma development is helpful for

prevention of systemic dissemination and follow-up can improve the quality of life of patients.

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