Primary B-Cell Mucosa-Associated Lymphoid Tissue Lymphoma of the Hard Palate and Parotid Gland: Report of One Case and Review of the Literature

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Abstract

A 61-year-old woman was admitted to our hospital with an ulcerated palate mass and swelling of the right parotid gland. Incisional biopsy from the hard palate revealed an extranodal marginal zone B-cell lymphoma, also called mucosa-associated lymphoid tissue (MALT) lymphoma. Final diagnosis was MALT lymphoma of the parotid gland with concomitant involvement of an extremely seldom site of involvement: the hard palate. To our knowledge, this report illustrates the first case of MALT lymphoma of the hard palate and parotid gland without an underlying autoimmune disease. Rituximab-based combination regimen (R-CHOP) provided complete remission with total regression of mass lesions at the hard palate and parotid gland. At 44-month follow-up, there is no disease relapse. We addressed the manifestations and management of MALT lymphoma patients with involvement of salivary gland and oral cavity.

Keywords: MALT lymphoma; Hard palate; Parotid gland

Introduction

Marginal zone lymphoma (MZL) is an indolent B-cell lymphoma that accounts for about 5-17% of all non-Hodgkin’s lymphomas (NHLs) in adults [1]. MZL arises from post-germinal center marginal zone B cells present in lymph nodes and extranodal tissues. The neoplastic cells share a similar immunophenotype: positive for B-cell markers CD19, CD20, and CD22, and negative for CD5, CD10, and usually CD23 [2-4]. According to the REAL/WHO classification systems, MZL comprises three subtypes: extranodal marginal zone B-cell lymphoma, also called mucosa-associated lymphoid tissue (MALT) lymphoma, nodal marginal zone B-cell lymphoma (NMZL) and splenic marginal zone B-cell lymphoma (SMZL) (+ villous lymphocytes). MALT lymphomas are the most common type of MZL, which constitute about 5% of all NHLs [5]. MALT lymphomas are divided into gastric and non-gastric MALT lymphomas based on the localization at initial diagnosis. The most common manifestation sites of non-gastric MALT lymphomas are the salivary glands, the thyroid, the upper airways, the lung, the ocular adnexa, the breast, the liver, the urothelial system, the skin, the dura and other soft tissues [1]. In the head and neck region except for the salivary glands, the development of this neoplasm is very rare [6]. Thus far, only few previous cases of MALT lymphoma with involvement of hard palate have been reported [6-14]. Herein, we report on a case of MALT lymphoma of the parotid gland with concomitant involvement of an extremely rare site of occurrence: the hard palate.

Case Report

A 61-year-old woman was admitted to the Department of Otolaryngology with a 1-year history of swelling in the right palatal region and problems with pronunciation and chewing. Also, she suffered from a painless, progressively enlarging mass in the right preauricular region. On physical examination, swelling of the right parotid gland (Fig. 1a) and a 2 × 2.5 cm mass with central ulceration on the right hard palate (Fig. 1b) were noted. She had no history of fever, weight loss or night sweats. No lymph nodes were palpated in the head and neck region. Blood count was as follows: hemoglobin 13 g/dL, total leukocyte count 6,240/mm³ (neutrophil 54%, lymphocyte 36%) and platelet 185,000/mm³. Biochemical tests showed normal lactate dehydrogenase (LDH), beta-2 microglobulin levels and protein electrophoresis was normal. Cervical magnetic resonance imaging (MRI) confirmed a 2 × 2.5 cm mass with central ulceration on the right hard palate (Fig. 1b) were noted. She had no history of fever, weight loss or night sweats. No lymph nodes were palpated in the head and neck region. Blood count was as follows: hemoglobin 13 g/dL, total leukocyte count 6,240/mm³ (neutrophil 54%, lymphocyte 36%) and platelet 185,000/mm³. Biochemical tests showed normal lactate dehydrogenase (LDH), beta-2 microglobulin levels and protein electrophoresis were normal. Cervical magnetic resonance imaging (MRI) confirmed a 2 × 2.5 cm mass on the right side of the hard palate and a 2.5 × 3.5 cm mass in the right parotid gland region (Fig. 2a, b and c). Incisional biopsy of the palatal mass revealed subepithelial infiltration of atypical centrocyte-like cells with or without clear cytoplasm that stained...
for CD20 and kappa light chain, and did not stain for CD5, CD10, CD23 and lambda light chain, suggesting marginal zone B-cell lineage (Fig. 3a, b). Further examination included hepatitis B, C, HIV testing, chest and abdominopelvic computed tomography (CT), bone marrow aspirate and biopsy, and gastroscopy with multiple biopsies, all of which revealed unremarkable findings. The final diagnosis was MALT lymphoma with involvement of two extralymphatic sites: parotid gland and hard palate. Screening for autoimmune disorders including Sjogren’s syndrome was negative. Because of multiple extranodal involvements, a multi-agent chemotherapy regimen, rituximab, cyclophosphamide, doxorubicin, vincristine, and methylprednisolone (R-CHOP) was started. After five cycles, the patient had improved quality of life through the recovery of orofacial functions such as pronunciation and chewing. After six cycles, mass arising from the right side of the hard palate almost totally disappeared and the ulceration totally regressed (Fig. 4a). Also, swelling on the right parotid gland significantly regressed. MRI confirmed the disappearance of the mass in the right palatal region (Fig. 4b) and the marked regression of the enlargement of the right parotid gland. Chemotherapy was completed up to eight cycles. She has been in complete remission (CR) without any evidence of recurrent lymphoma infiltration for the past 44 months.

Discussion

MZL is a rare type of NHL characterized by indolent nature with three subgroups: MALT lymphoma, NMZL and SMZL. A variety of factors including chronic infections (e.g. Helicobacter pylori, HCV, Campylobacter jejuni, Borrelia burgdorferi, and Chlamydia psittaci) and autoimmune diseases (e.g. rheumatoid arthritis, Sjogren’s syndrome, systemic lupus erythematosus and Wegener’s granulomatosis) have been reported to be associated with MZL [1]. MALT lymphomas are the most common subgroup of MZL and also account for a significant proportion of extranodal lymphomas [5, 6]. Isaacson and Wright in 1983 first described MALT lymphoma as a low grade B-cell lymphoma [15]. For MALT lymphomas, average age at diagnosis is 60 years with a slight female predominance [16]. MALT lymphomas occur most commonly in stomach and they can be found virtually in every organ including the intestine, salivary glands, thyroid, lung and orbit, and also though less frequently, the skin, urinary bladder and the gonads [17].

NHLs of the salivary gland account for only 1.7% of sali-
Primary B-Cell MALT Lymphoma

Primary B-cell MALT lymphoma is a type of non-Hodgkin lymphoma (NHL) characterized by chronic antigenic stimulation and immune hyperactivity. It typically involves extranodal sites, most commonly the salivary glands, stomach, and conjunctiva. The salivary gland involvement is usually due to chronic antigenic stimulation associated with Sjögren’s syndrome.

**Etiopathogenesis**

Primary B-cell MALT lymphomas are often associated with chronic antigenic stimulation, which can be triggered by persistent infections and/or autoimmune processes. The Helicobacter pylori infection is known to induce chronic gastritis, which can lead to the development of gastric MALT lymphomas. Similarly, H. pylori infection has also been associated with a subset of non-gastric MALT lymphomas. In the case of salivary gland involvement, most salivary gland MALT lymphomas are thought to develop on the basis of chronic antigenic stimulation in the presence of Sjögren’s syndrome.

**Clinical Presentation**

In the oral cavity, MALT lymphomas are rare. Approximately 2% of all extranodal lymphomas involve the oral cavity, and the most common site of involvement is the oral cavity including the palate, gingiva, tongue, buccal mucosa, lips, and floor of the mouth. Primary lymphomas of the oral cavity in non-immunocompromised patients most commonly present as diffuse large B-cell lymphoma (DLBL). Mantle cell lymphoma, MALT lymphoma, Burkitt’s lymphoma, lymphomablastic lymphoma, peripheral T-cell lymphoma and anaplastic large cell lymphoma have also been reported. In a study by Kemp et al., 40 cases of oral cavity NHLs were evaluated, with most cases being B-cell lineage (98%), followed by follicular lymphoma (15%), MALT lymphoma (13%), plasma cell tumors (8%) and small lymphocytic lymphoma/chronic lymphocytic leukemia (5%).

**Imaging**

Histopathological findings of the palatal mass are shown in Figure 3. (a) Subepithelial infiltration of atypical centrocyte-like cells with or without clear cytoplasm (H&E stain, × 400). (b) Infiltrated cells in the hard palate with CD20 expression (H&E stain, × 400).

Figure 4. Case image and clinical findings after six cycles of chemotherapy. (a) Total regression of the ulcerated mass on the right hard palate. (b) Disappearance of the mass at the right palatal region on T1-weighted coronal MRI.

**Pathological Features**

- Subepithelial infiltration of atypical centrocyte-like cells with or without clear cytoplasm
- CD20 expression in infiltrated cells

**Clinical Outcomes**

Four to seven percent of patients with Sjögren’s syndrome develop primary B-cell MALT lymphoma of the hard palate. The described cases show a strong female predominance (9:1) and are mostly of older age. Four to seven percent of patients with Sjögren’s syndrome develop primary B-cell MALT lymphoma.
develop malignant B-cell lymphomas, 48-75% of which are MALT lymphomas [38, 39]. Sjogren’s syndrome plays a major role in the development of MALT lymphoma of the oral and maxillofacial region, most frequently being located in the parotid gland [40-42]. As depicted in Table 1, Sjogren’s syndrome was observed in one-third of MALT lymphoma patients with palatal involvement. Considering the importance of Sjogren’s syndrome, we screened and ruled out autoimmune disorders in our patient. The most frequent clinical appearance of palatal MALT lymphomas is non-tender yet rarely ulcerated mass [8]. To our knowledge, only two previous reports described ulcerated masses associated with palatal MALT lymphomas [1, 7]. Our patient also presented with ulceration located at the center of the hard palate. She had multiple extranodal involvements, hard palate and parotid gland, as reported in the two other cases [4, 6]. Our patient had no underlying autoimmune disease in contrast to the two aforementioned cases [4, 6]. MALT lymphoma in general is an indolent disease, with a 5-year overall survival rate of 86-95%. Patients with localized and disseminated disease show no significant difference in clinical course [24, 43]. The follow-up durations of MALT lymphoma patients with hard palate involvement were between 6 and 48 months; our case has the second longest follow-up duration (Table 1) [6-14]. One of the patients was lost to follow-up and one had succumbed to the disease due to relapse. There is no optimal treatment for MALT lymphomas because of their relative infrequency and heterogeneity in disease biology, clinical presentation and behavior. In non-gastric MALT lymphomas with symptomatic local disease, local treatment (surgery or radiotherapy) results in excellent disease control [44]. For symptomatic disseminated disease, chemotherapy has commonly been used, with 75% CR rate and 5-year event-free survival and overall survival rates of 50% and 75%, respectively [24, 43, 45-47]. More recently, anti-CD20 monoclonal antibody rituximab, which alone or in combination with chemotherapy demonstrated efficacy against B-cell lymphomas, has also been used effectively in MALT lymphomas [48-52]. Given the risk of occult disseminated disease, extensive workup procedures are needed in non-gastric MALT lymphomas including a staging system based on the Ann Arbor classification and the modification for primary gastric lymphoma by Musshoff [53, 54]. According to the aforementioned classification systems, patients were divided to three subgroups: localized disease, locally disseminated disease and disseminated disease. Since our patient had disseminated disease with involvement of multiple extranodal sites (hard palate and parotid gland), we administered rituximab-based chemotherapy. Of the other two reported disseminated MALT lymphomas with hard palate involvement, one was treated with chemotherapy and radiotherapy and the other with rituximab (Table 1). All patients with localized disease except one were treated with surgical excision of the mass on the hard palate while the single patient experienced spontaneous regression of the tumor (Table 1). Cases of spontaneous regression of several MALT lymphomas

| Case | Ref. | Age/sex | Autoimmune disease | Size (mm) | Location | Palatal ulceration | Treatment | Response | Outcome | FU |
|------|------|---------|-------------------|----------|----------|-------------------|-----------|----------|---------|-----|
| 1    | Tauber et al [6] | 71/F | NR | 20 | Hard + soft palate | Yes | Excision | CR | A | 4 years |
| 2    | Ayers et al [7] | 64/F | NR | NR | Hard palate | No | - | - | - | LTF |
| 3    | Manveen et al [8] | 40/M | No | 45 | Hard palate | No | Excision | CR | A | 6 months |
| 4    | Dunn et al [9] | 64/F | SS, scleroderma, cryoglobulinemia | 20 | Hard palate + parotid + nasopharynx + cervical LN | NR | Chemo + RT | Fourth CR | A | 57 months |
| 5    | Kolokotronis et al [10] | 73/F | No | NR | Hard palate | NR | Excision | RD | DOD | 15 months |
| 6    | Pijpe et al [11] | 42/F | SS | 20 | Hard palate + parotid | NR | Chemo (R) | CR | A | 6 months |
| 7    | Sakuma et al [12] | 70/F | SS | 17 | Hard palate | Yes | Spontaneous regression | CR | A | 38 months |
| 8    | Shah et al [13] | 55/F | NR | 19 | Hard + soft palate | No | Excision | CR | A | 2 years |
| 9    | Abe et al [14] | 64/F | No | 30 | Hard palate | No | Excision | - | - | - |
| 10   | Present case | 61/F | No | 25 | Hard palate + parotid | Yes | Chemo (R-CHOP) | CR | A | 44 months |

A: alive; CR: complete remission; DOD: died of disease; FU: follow-up; NR: not recorded; RD: relapsed disease; R: rituximab; Ref.: references; RT: radiation therapy; SS: Sjogren’s syndrome; LTF: lost to follow-up.
of the rectum and ocular adnexa have been reported [55, 56]. Of the described palatal MALT lymphomas, one showed CR after the biopsy (Table 1) [12]. The mechanisms for spontaneous regression of tumors can be explained by several factors: immune mediation, tumor inhibition by growth factors and/or cytokines, induction of differentiation, elimination of carcinogens, tumor necrosis or angiogenesis inhibition, psychological factors, apoptosis and epigenetic mechanisms [57, 58]. In the above-mentioned case, Sakuma et al speculated that traumatic effect and localized infection induced by the surgical intervention might have activated tumor immunity and hence provided spontaneous regression [12].

In conclusion, based on information synthesized from the literature review, extensive workup procedures, including history and physical examination, complete blood cell counts and basic biochemical studies including tests of renal and liver function, LDH and β2-microglobulin levels, protein electrophoresis; HIV, HCV, and HBV serologies; CT scans of the cervical region, chest, abdomen, and pelvis; bone marrow aspirate and biopsy; and gastroduodenal endoscopy with multiple biopsies to exclude a concomitant gastric involvement are mandatory in all MALT lymphomas because of the risk of occult disseminated disease. Current management guidelines recommend a “patient-tailored” approach taking into account the stage, site and clinical characteristics of the individual non-gastric MALT lymphoma patient. Therapeutic strategies for MALT lymphomas are not standardized due to the small number of cases described in the head and neck region. Herein, we described a rare MALT lymphoma patient of the hard palate with concomitant parotid gland involvement, who remained disease free for 44 months. In case of multiorgan involvement, systemic therapy with either chemotherapy or chemotherapy in combination with rituximab seems to be an appropriate option for MALT lymphoma of the head and neck region.

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