Asymptomatic marginal zone lymphoma of mucosa-associated lymphoid tissue in the hypopharynx, detected with esophagogastroduodenoscopy

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ABSTRACT
Mucosa-associated lymphoid tissue (MALT) lymphoma is a type of lymphoma that commonly originates in the gastrointestinal (GI) tract, and in rare instances may also occur in the head and neck region. In this report, we present a case of early stage, primary asymptomatic MALT lymphoma of the hypopharynx as detected by esophagogastroduodenoscopy (EGD). A 73-year-old man underwent EGD for an examination of the upper GI tract. At the left pyriform sinus, a swollen irregular mucosa was detected. Biopsy specimens confirmed histologically prominent proliferation of lymphocytes in the epithelium. Immunohistochemical analysis showed that the neoplastic lymphocytes were positive for CD20 and negative for CD3. Based on the other imaging studies, we diagnosed the lesion as a localized MALT lymphoma of the hypopharynx at Stage IA. In total, 46 Gy of radiotherapy was administered to the lesion. In the subsequent 5 years after the treatment, there have been no signs of recurrence.

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Introduction
Mucosa-associated lymphoid tissue (MALT) lymphoma is classified by the International Lymphoma Study Group and World Health Organization as a type of low-grade marginal zone B-cell lymphoma that arises at various extranodal sites [1–3]. MALT lymphomas most commonly originate in the gastrointestinal (GI) tract, including the stomach, small intestine and colon [4], and in rare instances, the head and neck region. The malignant potential of MALT lymphomas is generally lower than that of other extranodal lymphomas, resulting in a favorable prognosis. However, in the head and neck region, the detection of especially early stage lesions can be particularly challenging, and consequently outcomes tend to be poorer in comparison to lesions in other regions [5].

In this report, we describe a rare case of primary MALT lymphoma of the hypopharynx at early stage, detected by esophagogastroduodenoscopy (EGD). We also review the literature and discuss recent developments relating to the disease.

Case report
A 73-year-old man presented with mucosal irregularities of the esophagus, as detected by EGD at a different hospital. The patient did not display any symptoms associated with the head and neck region but had previously been diagnosed with tuberculosis of the lungs, left renal cancer, hepatocellular carcinoma and prostate cancer. All prior diseases had been controlled without complications or recurrence.

At the left pyriform sinus of the hypopharynx, endoscopy revealed a swollen irregular mucosa accompanied by white moss-like lesions at the surface with an abnormal vascular pattern (Figure 1(a,b)). Magnification and image-enhanced endoscopy showed tiny dots of vessels, which were clustered and consistent with a swollen mucosa but were present at a lower density than in squamous cell carcinomas (Figure 1(c,d)). We took some biopsies from the lesion during endoscopy and found no other findings in the esophagus, stomach or duodenum.

Histopathological specimens from the biopsies demonstrated prominent proliferation and dense

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infiltration of lymphocytes in the epithelium. The lymphocytes were differentiated into plasma cells, accompanied by Russell bodies (Figure 2(a,b)). Immunohistochemical analysis showed that the neoplastic lymphocytes were positive for CD20 but negative for CD3 (Figure 3(a,b)). Immunoglobulin lambda chain expression was higher than kappa chain expression in the plasmacytic cells (Figure 4(a,b)). The Ki-67 labeling index was approximately 20%.

Positron emission tomography (PET) demonstrated focal F-18 fluorodeoxyglucose (FDG) uptake in the left pyriform sinus, compatible with endoscopic findings, with no other uptake visualized (Figure 5). Blood test results indicated high levels of the serum soluble interleukin-2 receptor (634 U/mL), while the Helicobacter pylori IgG antibody test was negative. The results of the bone marrow aspiration were normal and negative for translocations t(11;18) and t(14;18).

We diagnosed the lesion according to the Ann Arbor Classification System as Stage IA localized MALT lymphoma of the hypopharynx. In collaboration with the Departments of Otolaryngology, Hematology, and Radiology, radiotherapy was administered to the lesion. Local irradiation to the left pyriform sinus was delivered with a total dose of 46 Gy/23 fractions, over the course of four-and-a-half weeks, treating 5 days a week. Four megavoltage (MV), photons were used with lateral opposed beams. The procedure of radiotherapy was completed without severe complications.

Three months after treatment, the first follow-up examination with PET revealed a disappearance in FDG uptake at the same site, and the absence of an irregular surface. Follow-up studies were continued for a period of 5 years using endoscopy and imaging examinations, including biopsy specimens taken from the same site, and there have been no signs of a recurrence of the disease (Figure 6).

Written informed consent was obtained from the patient for academic presentations, including this case report and accompanying images.

**Discussion**

MALT lymphomas originate at various extranodal sites, including the GI tract (50%), head and neck region (15%), lungs (14%), ocular adnexa (12%), skin (11%), thyroid (4%) and breasts (4%). Damage of the mucosa or epithelium by chronic inflammation, or an underlying autoimmune disorder, may be of significance in MALT lymphomas; for example, there is a
well-established association between *H. pylori* infection and MALT lymphomas of the stomach [6]. Several previously published reports have also suggested that MALT lymphomas of the larynx may be caused by chronic laryngitis, extraesophageal reflux disease, or *H. pylori* infection of the stomach [7,8]. Kania et al. described an incidence of laryngeal MALT lymphoma, which was successfully managed by a combination of surgical excision, reflux therapy and eradication of *H. pylori* [9–11]. The relationship between these conditions and MALT lymphomas of the head and neck region, however, remains unclear. In our case, the patient did not present with pharyngitis, gastroesophageal reflux disease, or a gastric *H. pylori* infection. The etiologic factors were unidentified, and we did not add treatments for reflux therapy or eradication of *H. pylori*.

MALT lymphomas occur in the head and neck region less frequently than in other sites [10]. Typically, they involve the ocular adnexa, major salivary glands, oral cavity, tonsils, nasopharynx, oropharynx, hypopharynx, larynx and thyroid gland [12]. Although Waldeyer’s ring is the most common site of primary non-Hodgkin’s lymphomas, the dense population of lymphocytes within results in a low incidence of MALT lymphomas around this region [13,14]. Only a few articles have reported cases with MALT lymphomas in the pharynx or larynx. Wenzel et al. reported the first incidence of MALT lymphoma involving the hypopharynx and conjunctiva [15]. Of the non-Hodgkin’s lymphomas in the head and neck region, only 11% are indolent, accounting for just 1% of all non-Hodgkin’s lymphomas [16], and more than 50% of patients with nongastric MALT lymphomas were found to have multiorgan involvement [17]. As most lesions are detected at advanced stages accompanied by lesions at multiple sites, and in challenging anatomical locations, radiotherapy and/or chemotherapy is a more preferable option than surgery for the management of head and neck MALT lymphomas.

In this case, when deciding radiotherapy as a treatment and its total dose of 46 Gy, we adopted previous articles, suggesting the dose more than 45 Gy for...
Figure 4. Immunohistochemical analysis results showed the tumor cells were strongly positive for (a) immunoglobulin lambda chain more than (b) immunoglobulin kappa chain (original magnification ×200).

preventing local relapse [18,19]. However, recent studies and guidelines have supported the theory that 30 Gy is adequate for indolent lymphoma in the pharynx [20]. As MALT lymphoma is not common in the pharynx, more reports with the series of dose-effect in radiotherapy are needed for the optimal dose to this area.

The difficulty in detecting head and neck MALT lymphomas at an early stage is the distinct lack of an established screening system for them, unlike neoplasms of the stomach. However, close monitoring by EGD in combination with GI screening can be considered an innovative breakthrough in the detection of head and neck neoplasms [21,22]. In our university as well, endoscopists have tried to improve the detection rate of head and neck neoplasms with new methods for diagnosis, such as the ‘U-turn method’ [23]. Through these applications, we have been able to detect a significant number of cases involving head and neck abnormalities, including early stage cancers and precancerous lesions. We believe that these efforts have also resulted in the early detection of the hypopharyngeal MALT lymphoma case described in this report.

In conclusion, hypopharyngeal MALT lymphomas represent rare clinical entities, especially at early stage diagnosis. As the opportunity arises for closer monitoring of the head and neck region by EGD, endoscopists will need to be able to detect abnormal findings in the mucosa of these regions as well.

Disclosure statement

No potential conflict of interest was reported by the authors.

Figure 5. Positron emission tomography (PET) image with F-18 fluorodeoxy glucose (FDG) accumulation localized in the left pyriform sinus of the hypopharynx, pointed with white arrow.

Figure 6. Endoscopy with the Valsalva maneuver showing no signs of recurrence following treatment.
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