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Case report

Mucosa-associated lymphoid tissue lymphoma with metachronous involvement of the palpebral conjunctiva and bronchus: A case report

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ABSTRACT

A 61-year-old woman with a history of palpebral conjunctival mucosa-associated lymphoid tissue (MALT) lymphoma, treated with rituximab, was referred to the authors' hospital after follow-up positron emission tomography/computed tomography revealed ^{18}F-fluoro-2-deoxy-D-glucose uptake in a tumor located in the left main bronchus. The diagnosis of MALT lymphoma was made by pathological and immunohistochemical findings homologous to previous palpebral conjunctival lesion via bronchoscopic biopsy. The disease was controlled with rituximab, cyclophosphamide, oncovin, and prednisolone (i.e., R-COP) chemotherapy. Although MALT lymphoma occurs in several organs, metachronous occurrence in the palpebral conjunctiva and bronchus is especially rare, and careful check-up is required to monitor for occurrence of systemic relapse.

1. Introduction

First described in 1983 [1], mucosa-associated lymphoid tissue (MALT) lymphoma is a low-grade B-cell lymphoma that originates from the marginal zone and epithelial tissues. MALT lymphoma arises most frequently in the gastrointestinal tract, but also occurs in the salivary glands, thyroid gland, and lung [2]. Pulmonary MALT lymphoma is a rare disease that accounts for < 1% of all malignant lymphomas. It is the most common histological subtype of lung lymphoma; nevertheless, MALT lymphomas in the bronchus are still rare [3]. The clinical course of MALT lymphoma is usually indolent, and the tendency to remain at the primary site and dissemination to other mucosal sites are poorly understood [4]. We report a case of bronchial MALT lymphoma in a patient with a history of palpebral conjunctival MALT lymphoma.

2. Case report

A 61-year-old woman first visited our hospital because of abnormal ^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG) uptake in the left main bronchus tumor on positron emission tomography/computed tomography (PET/CT). She had a history of palpebral conjunctival MALT lymphoma treated with rituximab 9 years before visiting. She had no other relevant medical history, except for palpebral conjunctival MALT lymphoma, and no episodes of chronic autoimmune disease. During examination for palpebral conjunctival MALT lymphoma, esophagogastroduodenoscopy revealed no significant lesion, and *Helicobacter pylori* infection was negative according to the results of a biopsy culture. Laboratory findings of lactate dehydrogenase (LDH) and soluble interleukin-2 receptor (sIL-2R) levels were within the normal range at that time. She had no history of smoking or excessive alcohol consumption. Nine years after a routine systematic check-up of a MALT lymphoma, she was referred to our hospital for further investigation.

Findings on a physical examination were unremarkable. Laboratory tests for LDH, tumor markers (CEA, SCC, and ProGRP) and others, were within normal levels. Chest CT revealed a tumor, 13 mm in size, in the inlet of the left main bronchus (Fig. 1), and an 8 mm nodule in the lingular segment of the left lung. PET/CT revealed abnormal FDG uptake (maximum standardized uptake value, 4.1) in the left main bronchus tumor, but not in the palpebral conjunctiva, with no other abnormal uptake (Fig. 2). Subsequent flexible bronchoscopy revealed a polypoid tumor in the left second carina, in which mucosal edema and over-swelled blood vessels were observed (Fig. 3). There were also small polypoid lesions in the right middle and lower bronchus; biopsy from all tumors was performed. Histologically, an increased number of

Abbreviations: CEA, Carcinoembryonic antigen; FDG, ^{18}F-fluoro-2-deoxy-D-glucose; SCC, Squamous cell carcinoma antigen; ProGRP, Pro gastrin releasing peptide; MALT, Mucosa-associated lymphoid tissue; PET/CT, positron emission tomography/computed tomography

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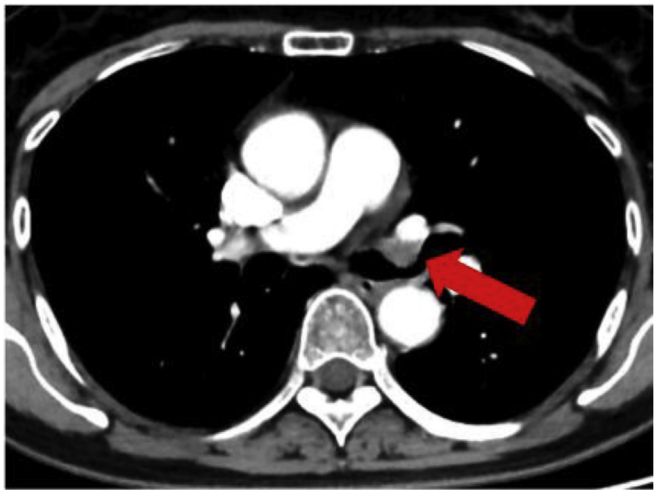

Fig. 1. Contrast-enhanced computed tomography demonstrating a protuberant tumor in the lumen of the left main bronchus (arrow).

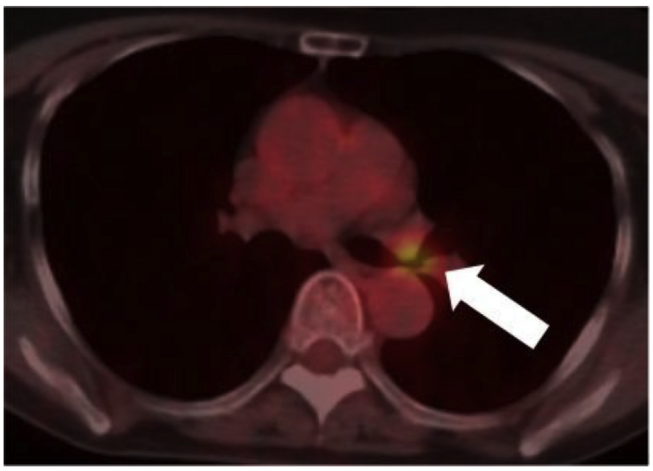

Fig. 2. Positron emission tomography/computed tomography revealing higher accumulation of ^{18}F-fluoro-2-deoxy-D-glucose in the lumen of the left main bronchus (maximum standardized uptake value = 4.1) coinciding with tumor (arrow).

small-to medium-size lymphocytes were observed around germinal center-like structures and partially infiltrated the bronchial epithelium, forming lymphoepithelial lesions. The histological appearance of the bronchus tumors were similar to past palpebral conjunctival MALT lymphoma (Fig. 4A–D). Immunohistochemical staining of the bronchial tumor was positive for CD79a, CD20, and BCL-2 (Fig. 4E and F), and negative for CD3, CD5, CD10, and cyclin D1; the expression of κ-to-λ ratios were not significant. These findings were consistent with the diagnosis of MALT lymphoma. The results of immunohistochemical staining of the bronchial lesion and palpebral conjunctival lesion were homologous. Furthermore, polymerase chain reaction (PCR) analysis of formalin-fixed paraffin-embedded sections was performed. The result of the specimen of the left main bronchus lesion revealed immunoglobulin heavy chain (IgH) gene rearrangement, although not in the previous palpebral conjunctival lesion. Fluorescence in situ hybridization detected no *API2-MALT1* fusion gene for either lesion. Despite the lack of genetic evidence, bronchial MALT lymphoma was diagnosed from the histological and immunohistochemical findings.

Because the MALT lymphoma was present in bilateral bronchial lesions from CT imaging and bronchoscopy, PET/CT demonstrated no uptake in other organs, and the results of bone marrow biopsy yielded no findings, she received treatment with rituximab, cyclophosphamide,

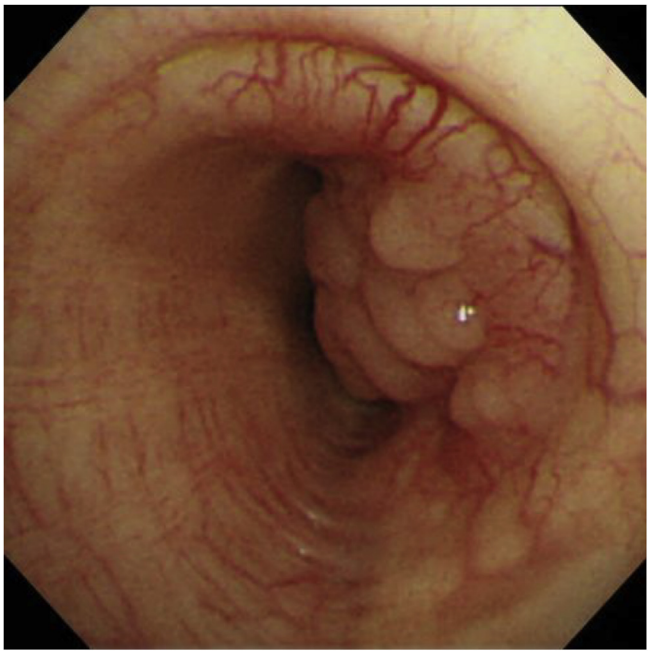

Fig. 3. Bronchoscopic view revealing multiple polypoid-surface tumors on the luminal surface of the left main bronchus.

oncovin, and prednisolone (R-COP). After receiving 6 courses of chemotherapy, the tumor was controlled, and the patient is undergoing follow-up as an outpatient given the good response.

3. Discussion

MALT lymphoma is a low-grade B-cell lymphoma, accounting for 7.6% of all non-Hodgkin lymphomas, with a 5-year survival rate of 88.7% [5,6]. Primary pulmonary MALT lymphoma accounts for 3.6% of all extranodal lymphomas and 0.4% of non-Hodgkin lymphomas [7]. Although the etiology of MALT lymphomas is not fully understood, several factors, such as autoimmune diseases, including Sjögren syndrome, and several infections, are believed to be correlated with disease development [8]. MALT lymphoma is regarded to be an indolent disease; however, there have been reports describing a substantial rate of systemic relapse [9]. Therefore, in our case, MALT lymphoma of both the palpebral conjunctiva and the bronchus was believed to be of the same origin; nevertheless, careful follow-up and treatment of MALT lymphoma are warranted.

Pathological features of MALT lymphoma include germinal center-like structures in lymphoid follicles, the proliferation of centrocyte-like cells, and the formation of lymphoepithelial lesions. Immunostaining is positive for CD20, negative for CD5, CD10, and cyclin D1. In this case, pathological findings of the bronchial tumor were consistent with MALT lymphoma, and IgH rearrangement was detected. Pathological findings of the palpebral conjunctival lesion and the bronchus were homologous. However, IgH rearrangement was not detected in the palpebral conjunctival lesion. The *API2-MALT1* fusion gene, the most common chromosomal abnormality in MALT lymphoma [10,11], was negative for both the bronchus and palpebral conjunctival lesions. According to genetic analysis in this case, we could not confirm whether both bronchus and palpebral conjunctival lesions occurred metachronously from an identical clone. However, histological appearances were similar; therefore, we speculated both lesions derived from the same origin.

Previous reports have demonstrated that MALT lymphomas are often observed in multiple or disseminated organs. Yoshino et al. described 7 cases of multiorgan MALT lymphoma (4 cases at initial diagnosis and 3 during the clinical course) in an analysis of 304 cases.

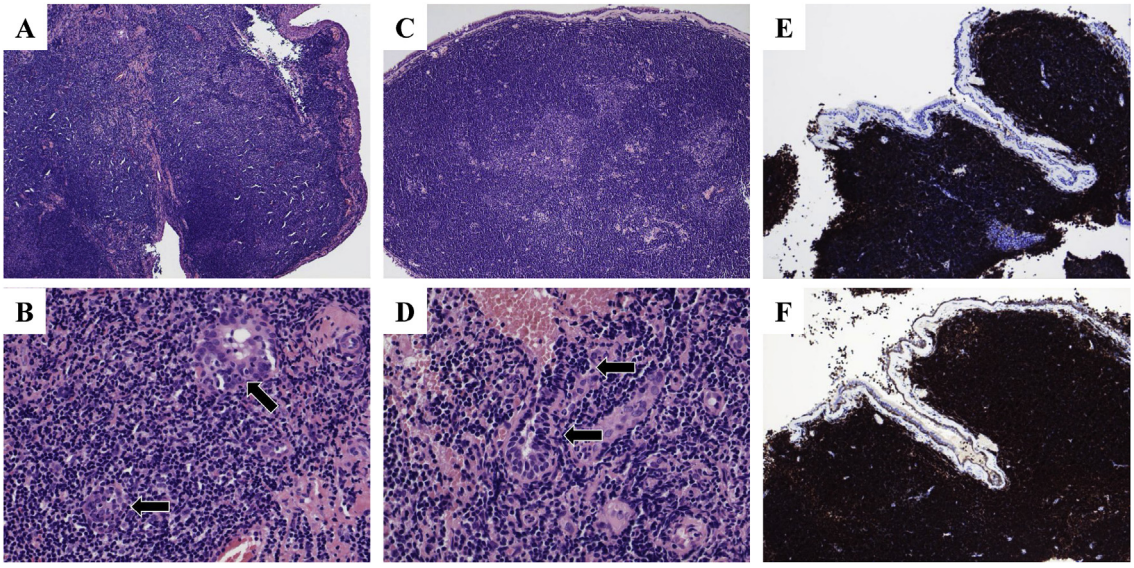

Fig. 4. (A) Histological findings from the palpebral conjunctival lesion. Diffuse proliferation of atypical lymphoid cells reaching the palpebral conjunctival epithelium (hematoxylin-eosin stain, original magnification ×40). **(B)** Small- and medium-size atypical lymphocytes infiltrating the adrenal glandular epithelium, forming lymphoepithelial lesions (arrow) (hematoxylin-eosin stain, original magnification ×400). **(C)** Histological findings from the bronchial lesion. Diffuse proliferation of atypical lymphoid cells surrounding the lymphoid follicles (hematoxylin-eosin stain, original magnification ×100). **(D)** Small- and medium-size atypical lymphocytes infiltrating the bronchial epithelium, forming lymphoepithelial lesions (arrow) (hematoxylin-eosin stain, original magnification ×400). **(E)** Immunohistochemical staining for CD79a was strongly positive in lymphocytic tumor cells infiltrating under the bronchial mucosa (CD79a stain, original magnification ×200). **(F)** Immunohistochemical staining for BCL-2 was also positive in lymphocytic tumor cells infiltrating under the bronchial mucosa (BCL-2 stain, original magnification ×200).

From the report, monoclonal immunoglobulin gene rearrangements in 5 of the 7 cases were identical; therefore, it is highly possible that multiorgan MALT lymphomas were derived from the same clone [12]. Similarly, Thiebelmont et al. reported 54 cases in 158 cases, and Raderer et al., reported 52 cases in 140 cases of multiorgan MALT lymphomas [9,13]. Raderer et al. detected 28 cases of genetic aberrations of the *API2-MALT1* gene (19 cases of gastric MALT lymphoma and 9 cases of non-gastric MALT lymphoma including lung). In gastric MALT lymphoma, the presence of the *API2-MALT1* fusion gene may be associated with disease dissemination [9]. Only a small number of studies have investigated non-gastric MALT lymphoma; further experience and studies are, therefore, warranted. To our knowledge, the present report describes the first case of MALT lymphoma with metachronous involvement of palpebral conjunctiva and bronchus, although we could not detect the *API2-MALT1* fusion gene in both lesions; thus, more detailed investigation is required.

Standard therapy for primary lung MALT lymphoma has yet to be established [14]. Surgical resection may be suggested for the local lesion, and radiation and chemotherapy can be recommended for unresectable tumors [15]. In this case, rituximab was used for the palpebral conjunctival MALT lymphoma, which has become a part of standard therapy [16]. R-COP therapy was performed due to the positive CD20 result in the bronchial lesion, and the tumor size was reduced in due course without recurrence. MALT lymphomas usually take an indolent clinical course and have a relatively good prognosis; however, careful follow-up is essential because some studies have reported transformation to high-grade lymphoma [17].

In conclusion, we encountered a case of bronchial MALT lymphoma that occurred after treatment of palpebral conjunctival MALT lymphoma 9 years previously. Both lesions could not be verified from the same clone; however, pathological findings were identical. As reported, MALT lymphoma is a multiorgan disease; therefore, systemic check-up and genetic investigation should be performed after MALT lymphomas are detected.

Conflicts of interest

The authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmcr.2018.12.004.

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