Case report of *API2-MALT1* fusion-positive MALT lymphoma arising from bilateral submandibular glands with no evidence of autoimmune syndromes

Kenichiro Ishibashi, DDS, PhD,[a,b] Kosuke Saida, DDS, PhD,[c] Masashi Kimura, DDS, PhD,[b] Shusuke Nishiwaki, DDS,[b] Hideaki Tsuji, DDS,[b] and Masahiro Umemura, DDS, PhD[b]

Mucosa-associated lymphoid tissue (MALT) lymphoma arising from the salivary glands is usually associated with chronic infection or autoimmune syndromes, such as primary Sjogren syndrome. The occurrence of *t(11;18)/API2-MALT1* is rare in salivary MALT lymphoma. Here we describe a case of *API2-MALT1* fusion-positive MALT lymphoma of the bilateral submandibular glands with no evidence of autoimmune syndromes. A 70-year-old man complained of a painless swelling in the bilateral submandibular gland. Serology examination results were negative for anti-SSA and anti-SSB. His right submandibular gland was dissected, and he was diagnosed with MALT lymphoma with the *API2-MALT1* fusion gene. Positron emission tomography/computed tomography scanning indicated mild fluorine-18-fluorodeoxyglucose uptake in the left submandibular gland and liver. He was treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone. After 6 years, the patient is alive and disease free. In the present case, the patient with *API2-MALT1* fusion-positive MALT lymphoma had a good outcome despite the advanced clinical stage. (Oral Surg Oral Med Oral Pathol Oral Radiol 2020;130:e294−e300)

Mucosa-associated lymphoid tissue (MALT) lymphoma is defined as the extranodal presentation of low-grade B-cell lymphoma in organs normally lacking lymphoid tissue, such as the stomach, lungs, ocular adnexa, and salivary glands.[1] In the salivary glands, MALT lymphoma development is strongly influenced by the presence of Sjogren syndrome (SjS) and infection with the hepatitis C virus (HCV).[2,3] According to Vazquez et al.,[4] MALT lymphoma of the submandibular gland accounts for 15% of cases of MALT lymphoma of the salivary glands. Furthermore, the incidence of MALT lymphomas occurring in bilateral submandibular glands accounts for less than 1% of cases of MALT lymphomas of the salivary glands.

Recurrent genetic alterations commonly occurring in cases of MALT lymphoma include trisomies 3 and 18 and translocations such as t(11;18)(q21;q21)/*API2-MALT1*, t(1;14)(p22;q32)/*BCL10-IGH*, and t(14;18)(q32;q21)/*IGH-MALT1*. Although previous studies have described the frequencies of such specific genetic alterations in cases of MALT lymphoma of the salivary gland,[5] no reports currently exist on the relationship between these specific genetic alterations and the clinicopathologic features of salivary gland MALT lymphomas.

To the best of our knowledge, this is the first case of *API2-MALT1* fusion-positive MALT lymphoma of the bilateral submandibular glands with no evidence of autoimmune disorders or HCV infection. To determine the most effective treatment protocol, it is important to differentiate salivary MALT lymphoma from malignant tumors and similar diseases (such as immunoglobulin G4 (IgG4)−related sialadenitis, SjS, sarcoidosis, and Kimura disease). Therefore we have also described the clinicopathologic features and diagnostic difficulties surrounding *API2-MALT1* fusion-positive MALT lymphoma arising from the bilateral submandibular glands.

CASE DESCRIPTION AND RESULTS

Written informed consent was obtained from the patient for the publication of this report and any accompanying images.

A 70-year-old male patient was referred to the Department of Oral and Maxillofacial Surgery, Ogaki Municipal Hospital, as a result of enlargement of the bilateral submandibular glands. The patient presented with painless bilateral submandibular masses, which had started to grow 1 month before the consultation (Figure 1). He had no previous medical history and was not on any medication. The patient complained of a dry mouth and a sensation of dyspnea. Intraoral examination indicated low salivary flow, and clinical examination indicated firm, movable masses in the bilateral submandibular area, with the right side being especially swollen. A contrast computed tomography (CT) scan identified enlarged bilateral submandibular glands (Figure 2A) with no evidence of significantly enlarged lymph nodes. The right and left submandibular masses measured 46 mm × 25 mm and 40 mm × 20 mm, respectively. Magnetic resonance imaging (MRI) further indicated enlargement of the submandibular glands, with homogeneous mild hyperintensity on T2-weighted images and homogeneous mild to moderate hypointensity on T1-weighted images

[a]Department of Maxillofacial Surgery, School of Dentistry, Aichi Gakuin University, Nagoya, Japan.
[b]Oral and Maxillofacial Surgery, Ogaki Municipal Hospital, Ogaki, Japan.
[c]Oral and Maxillofacial Surgery, Ichinomiya Municipal Hospital, Ichinomiya, Japan.
Received for publication Aug 2, 2019; returned for revision Dec 17, 2019; accepted for publication Dec 29, 2019.

2212-4403/$-see front matter
https://doi.org/10.1016/j.oooo.2019.12.018

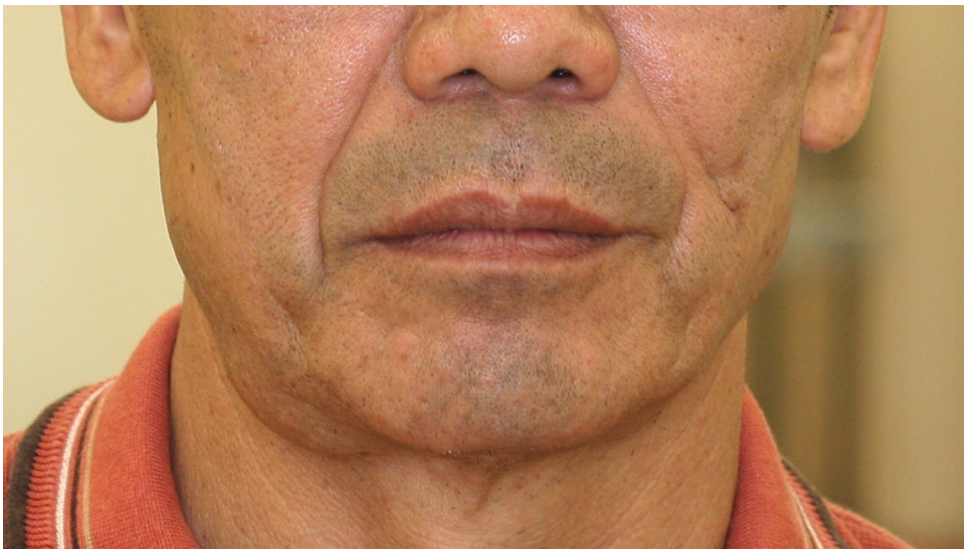

Fig. 1. Preoperative photo showing bilateral submandibular masses. The right submandibular region was found to be more swollen than the left region.

(Figure 2B–D). ^{99m}Tc-pertechnetate scintigraphy suggested that submandibular gland functions were lower than those of the parotid gland with lemon juice (Figure 3). A blood test indicated normal levels of leucocytes (5850 μL; normal range, 3500–9900 μL), lactate dehydrogenase (202 IU/L; normal range, 130–250 IU/L), IgG (977 mg/dL; normal range, 870–1700 mg/dL); IgG4 (17 mg/dL; normal range, 4–108 mg/dL), IgM (36 mg/dL; normal range, 35–220 mg/dL), and C4 (35 mg/dL; normal range, 17–45 mg/dL); but decreased levels of IgA (98 mg/dL; normal range, 110–410 mg/dL) and C3 (82 mg/dL; normal range, 86–160 mg/dL). Elevated levels of soluble interleukin 2 receptor (796 U/mL; normal range, 122–496 U/mL) were also identified. The tests for antinuclear antibodies, anti-SSA, and anti-SSB were all negative, as were the results of Schirmer's test and salivary gland scintigraphy (Figure 3). His serum was negative for anti–HCV antibody.

Although this submandibular mass was clinically suspected to be a salivary gland tumor, a lymphoproliferative lesion, sarcoidosis, Kimura disease, or IgG4-associated sialadenitis were also considered. Fine-needle aspiration cytology (FNAC) indicated small lymphocytes with no evidence of epithelial cells or any round to irregularly shaped nuclei or small nucleoli. Removal of the right submandibular gland was performed as an excisional biopsy. Histopathologically, dense and diffuse infiltration by small centrocyte-like neoplastic lymphoid cells was identified with hematoxylin and eosin (H&E) staining, with the associated formation of abundant lymphoepithelial lesions. Monocytoid B cells with paler cytoplasm surrounding the lymphoepithelial lesions were also found (Figure 4B). Immunohistochemistry indicated that the neoplastic cells were positive for CD79a, CD20, and BCL-2. Lymphoepithelial lesions were positive for AE1/AE3. In contrast, CD10, cyclin D1, CD5, and CD3 stains were all negative (Figure 4). An *API2-MALT1* translocation was detected in the biopsy specimen using reverse-transcription polymerase chain reaction. Fluorescence in situ hybridization analysis using a MALT (18q21) break probe (Kreatech Diagnostics, Amsterdam, Netherlands) found that lymphoid cells were positive for a *MALT1* split (Figure 5). Taken together, histologic, immunohistochemical, and genetic analyses led to a diagnosis of MALT lymphoma of the submandibular gland.

Disease staging was performed through the use of a fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/CT scan (PET/CT), which indicated mild ^{18}F-FDG uptake in the left submandibular gland and liver (Figure 6). The results from the bone marrow biopsy specimen and aspirate were both negative for lymphoproliferative disease involvement. According to the Lugano modification of the Ann Arbor scale, stage IV was compatible with the initial diagnosis.

After diagnosis, the patient was treated weekly with 6 courses of rituximab (Rituxan®, Zenyaku Kogyo Company, Tokyo, Japan), cyclophosphamide (Endoxan®, Shionogi, Osaka, Japan), doxorubicin (Adriacin®, Aspen Japan, Tokyo, Japan), vincristine (Oncovin®, Nippon Kayaku, Tokyo, Japan), and prednisone (Predonine®, Shionogi, Osaka, Japan) (R-CHOP). No serious adverse effects were identified. A PET/CT scan performed after

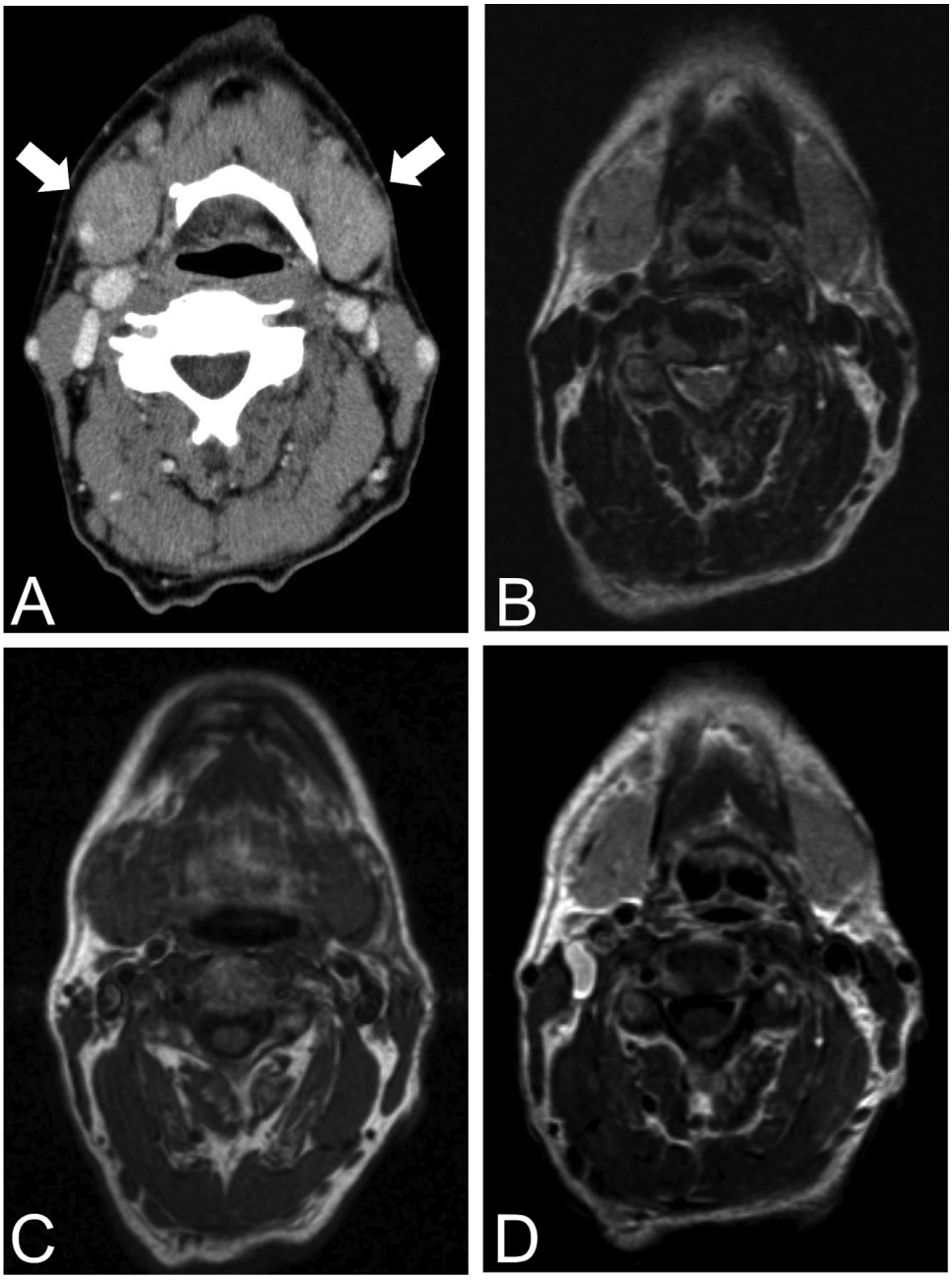

Fig. 2. Imaging findings before removal of the submandibular gland. **(A)** Contrast computed tomography scan. Arrows indicate swelling of the bilateral submandibular glands. **(B−D)** Magnetic resonance (MR) images showing enlargement of the bilateral submandibular gland, with homogeneous mild hyperintensity seen on T2-weighted images **(B)**, homogeneous mild to moderate hypointensity seen on T1-weighted images **(C)**, and mild homogeneous enhancement seen on contrast-enhanced MR images **(D)**.

completion of chemotherapy confirmed that there was no remaining disease. He has been in complete remission for the past 6 years with no evidence of recurrent lymphoma infiltration.

DISCUSSION

The salivary glands are the second most common site for MALT lymphoma occurrence. Although the parotid glands account for around 80% of salivary gland MALT lymphomas, the submandibular gland is a rare site.[6] Furthermore, previous reports have indicated that between 3% and 36% of salivary MALT lymphoma cases occur in bilateral or multiple salivary glands.[2,4,6] Salivary MALT lymphoma is generally associated with either autoimmune disease (such as SjS) or HCV infection.[2] The process of lymphomagenesis comprises multiple steps and encompasses mechanisms of antigen-driven selection of the B-cell receptor with

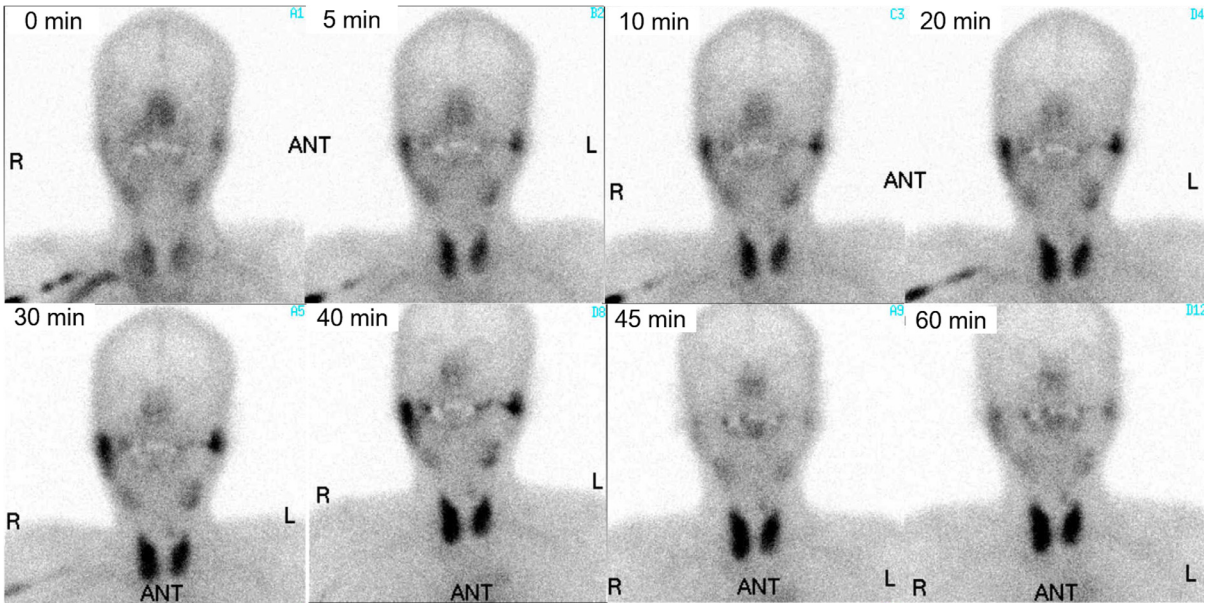

Fig. 3. ^{99m}Tc-pertechnetate scintigraphy shows satisfactory tracer accumulation in the bilateral parotid glands, but decreased accumulation in the submandibular glands, before lemon juice stimulation. Tracer washout at 40 minutes after lemon juice stimulation was identified in the parotid glands. *ANT,* anterior.

rheumatoid factor activity and various genetic contributors implicated in B-cell proliferation, cell growth, and cell cycle control, enhanced by a complex milieu of cytokines and trophic agents that are abundant within the inflammatory lesion of minor salivary glands in patients with SjS.[7,8] However, some studies have described specific recurrent translocations that play a critical role in MALT lymphoma development.[1] Three recurrent translocations are seen in a subset of MALT lymphoma, namely t(14;18)(q32;q21)/*IGH-MALT1*, t(1;14)(p22;q32)/*BCL10-IGH*, and t(11;18)(q21;q21)/*API2-MALT1*, all of which can activate both the canonical and noncanonical nuclear factor κB pathways. However, these recurrent translocations in MALT

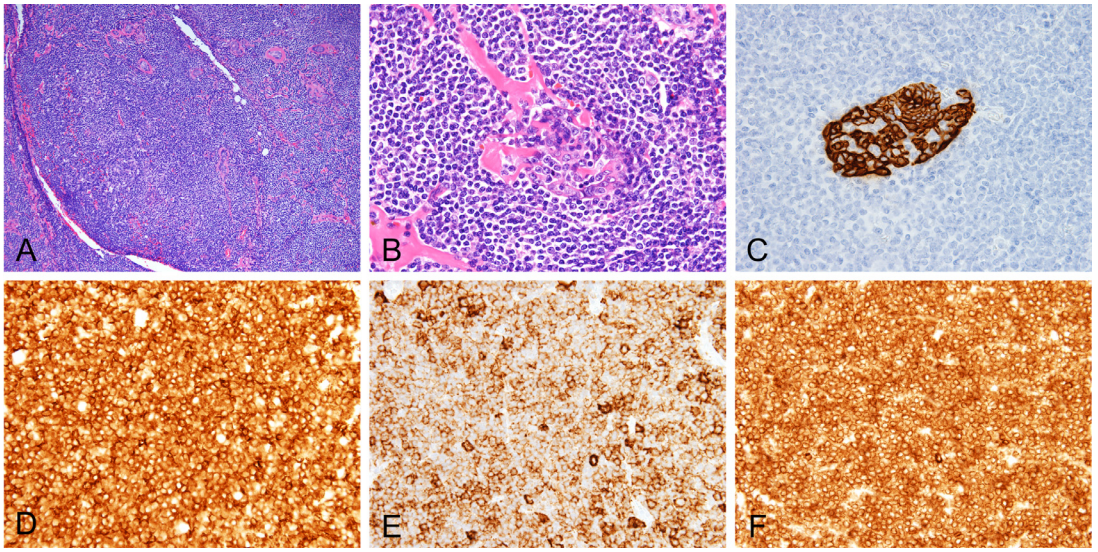

Fig. 4. Histologic findings of the right submandibular gland. **(A)** Mucosa-associated lymphoid tissue (MALT) lymphoma of the right submandibular gland. A dense and diffuse infiltration by small centrocyte-like neoplastic lymphoid cells was identified when stained with hematoxylin and eosin (H&E) in low-power view. **(B)** Organized lymphoid follicle and lymphoepithelial islands were also identified. Monocytoid B cells with paler cytoplasm were located around the lymphoepithelial lesions (H&E). **(C)** Lymphoepithelial lesions were positive for AE1/AE3. **(D)** Neoplastic MALT lymphoma cells were positive for BCL-2, **(E)** CD20, and **(F)** CD79a. *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM05691.*

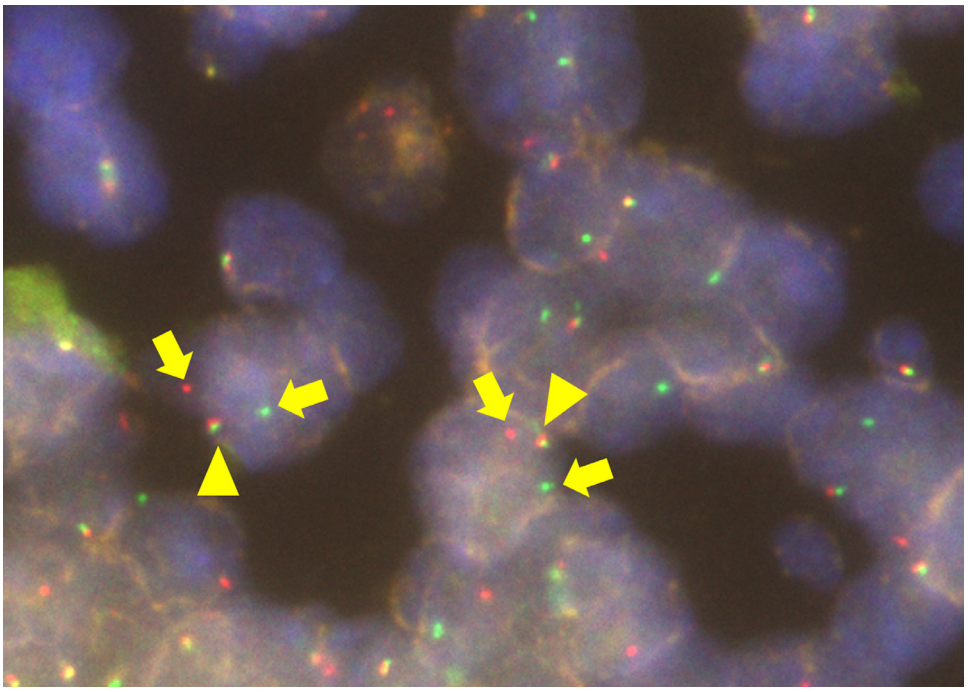

Fig. 5. Fluorescence in situ hybridization analysis of the right submandibular gland for the *MALT1* gene split. Arrows indicate split signals. Arrowheads indicate unsplit *MALT1* genes.

lymphoma are less common in the salivary glands than in the lungs, stomach, and ocular adnexa. To our knowledge, no previous reports exist on *API-MALT1* fusion-positive MALT lymphomas of the bilateral submandibular glands with no evidence of autoimmune disorders or HCV. This case report describes the diagnostic difficulty and clinicopathologic features of our case.

The differential diagnosis for MALT lymphomas in the bilateral submandibular gland includes salivary gland carcinoma, viral infections, sialolithiasis, IgG4-related sialadenitis, SjS, sarcoidosis, and Kimura disease.[9] The hemogram indicated no leukocytosis. Therefore, it is less likely that the submandibular mass resulted from infectious diseases. Laboratory findings of this patient showed that the serum levels of IgG4, IgE, anti-SSA, and anti-SSB were within normal limits, making the diagnosis of IgG4-related sialadenitis, and SjS unlikely. Blood examination is useful for ruling out viral infection, acute inflammation, and autoimmune disease of the salivary glands. CT scan did not reveal any suspected salivary stones. Previous studies featuring MRI have noted that salivary gland MALT lymphomas were occasionally accompanied by multiple cyst formation and ill-demarcated margins.[10] Diffusion weighted MRI can be effective for accurate diagnosis through its low-contrast enhancing capacity in both solid and cystic tumor regions.[10] In the present case, intraparenchymal solid nodules, rather than cystic regions, were detected in the submandibular gland during MRI. Considering that FNAC reported only small lymphocytes, FNAC alone was unable to provide a definitive diagnosis of salivary MALT lymphoma. Lymphomas, in general, are difficult to diagnose by FNAC alone because of overlapping morphologic features and the lack of tissue architecture.[11] Ultimately, an excisional biopsy of the submandibular gland was performed, with histopathologic examination, immunohistochemistry features, and the *MALT1* split signal from fluorescence in situ hybridization analysis leading to salivary gland MALT lymphoma diagnosis. In such cases, excisional biopsy of the submandibular gland is still the gold standard method for the definitive diagnosis of MALT lymphoma.

One of the clinical signs of this patient with *API2-MALT1* fusion-positive salivary MALT lymphoma was hyposalivation at the initial visit. The cause of his hyposalivation was unlikely to be polypharmacy because the patient had no previous medical history and was not on any medication. According to ^{99m}Tc-pertechnetate scintigraphy with lemon juice, the decreased function was identified in only the bilateral submandibular glands, and the salivary flow of parotid was noted to be normal. Therefore the cause of hyposalivation was considered to be a submandibular gland tumor.[12]

The presentation of *API2-MALT1* fusion-positive salivary gland MALT lymphomas has not yet been clarified. Previous research has established that *API2-MALT1* fusion involvement is very low in MALT lymphomas of the salivary gland[1,13,14] compared with the lung,

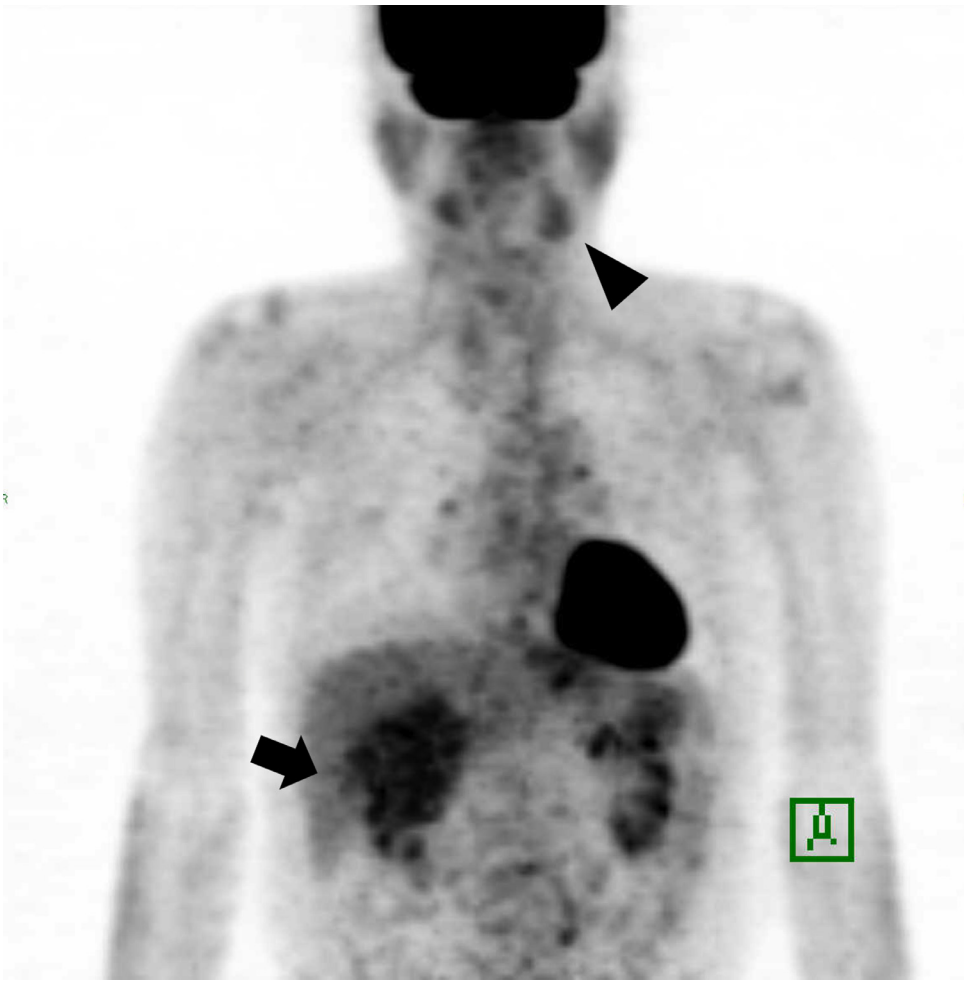

Fig. 6. 18-Fluorodeoxyglucose positron emission tomography (FDG-PET) performed before treatment. 18-FDG-PET indicated multiple abnormal accumulations in the submandibular glands (arrowheads) and liver (arrow).

stomach, and colorectum. However, there are few studies on the association between clinicopathologic features and the presence of this specific fusion gene in salivary MALT lymphoma. In gastric MALT lymphomas, *API2-MALT1* fusion was found to be clinicopathologically associated with a normal serum lactate dehydrogenase level, exclusively low-grade tumor histology, and a stable clinical course.[15] In addition, the number of patients testing positive for *API2-MALT1* fusion transcripts was significantly higher in patients with multiple lesions than in those with a single gastric lesion.[16] *API2-MALT1* fusion-positive gastric and pulmonary MALT lymphomas are entirely independent of chronic inflammation. Therefore it is suggested that fusion-positive tumors of the lung and stomach should be treated as distinct subgroups of MALT lymphomas.[17] In the present case, serum levels were within normal limits, and histologic features were low grade. Our workup indicated that MALT lymphomas were present in multiple sites: The bilateral submandibular glands and the liver. Despite his advanced clinical stage, the patient followed a stable clinical course. The clinicopathologic features of our patient were similar to those of *API2-MALT1* fusion-positive gastric MALT lymphomas. Our patient had no history or evidence of primary SjS or HCV infection. Similar to suggestions by other authors of fusion-positive MALT lymphoma in other sites, we suspected that this case of *API2-MALT1* fusion-positive MALT lymphoma of the submandibular glands constituted a distinct subgroup.

No previous cases of bilateral salivary MALT lymphomas with an *API2-MALT1* fusion gene have been reported. Considering that the treatment strategies for salivary MALT lymphomas are still controversial, multidisciplinary teams of oncology specialists, including hematologists and oral and maxillofacial surgeons, are required for the diagnosis and management of salivary MALT lymphoma. In our case the right submandibular gland was initially removed, with the excised specimen being useful to confirm the diagnosis of salivary MALT lymphoma. Therefore, salivary gland MALT lymphoma should be considered as a differential

diagnosis for patients presenting with bilateral swollen submandibular glands, even with no evidence of autoimmune disease or HCV infection. Our report suggests that (1) the *API2-MALT1* fusion-positive salivary gland MALT lymphoma may develop in the bilateral salivary glands or presents as multifocal lesions and (2) the prognosis is good despite the clinical stage. More case reports and further examinations are required, however, to fully clarify the clinicopathologic features of *API2-MALT1* fusion-positive MALT lymphomas arising from the salivary glands.

DISCLOSURE

There are no conflicts of interest to declare.

FUNDING

This work was supported in part by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology (MEXT) of Japan (17 K18213 to K. Ishibashi).

REFERENCES

1. Inagaki H. Mucosa-associated lymphoid tissue lymphoma: molecular pathogenesis and clinicopathological significance. *Pathol Int*. 2007;57:474-484.
2. Ambrosetti A, Zanotti R, Pattaro C, et al. Most cases of primary salivary mucosa−associated lymphoid tissue lymphoma are associated either with Sjoegren syndrome or hepatitis C virus infection. *Br J Haematol*. 2004;126:43-49.
3. Keszler A, Adler LI, Gandolfo MS, et al. MALT lymphoma in labial salivary gland biopsy from Sjogren syndrome: importance of follow-up in early detection. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2013;115:e28-e33.
4. Vazquez A, Khan MN, Sanghvi S, et al. Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue of the salivary glands: a population-based study from 1994 to 2009. *Head Neck*. 2015;37:18-22.
5. Zhou Y, Ye H, Martin-Subero JI, et al. The pattern of genomic gains in salivary gland MALT lymphomas. *Haematologica*. 2007;92:921-927.
6. Jackson AE, Mian M, Kalpadakis C, et al. Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue of the salivary glands: a multicenter, international experience of 248 patients (IELSG 41). *Oncologist*. 2015;20:1149-1153.
7. Goules AV, Tzioufas AG. Lymphomagenesis in Sjogren's syndrome: predictive biomarkers towards precision medicine. *Autoimmun Rev*. 2019;18:137-143.
8. Nocturne G, Mariette X. Sjögren syndrome−associated lymphomas: an update on pathogenesis and management. *Br J Haematol*. 2015;168:317-327.
9. Li TJ, Chen XM, Wang SZ, Fan MW, Semba I, Kitano M. Kimura's disease: a clinicopathologic study of 54 Chinese patients. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1996;82:549-555.
10. Kato H, Kanematsu M, Goto H, et al. Mucosa-associated lymphoid tissue lymphoma of the salivary glands: MR imaging findings including diffusion-weighted imaging. *Eur J Radiol*. 2012;81:e612-e617.
11. Dispenza F, Cicero G, Mortellaro G, Marchese D, Kulamarva G, Dispenza C. Primary non-Hodgkins lymphoma of the parotid gland. *Braz J Otorhinolaryngol*. 2011;77:639-644.
12. Napeñas JJ, Brennan MT, Fox PC. Diagnosis and treatment of xerostomia (dry mouth). *Odontology*. 2009;97:76-83.
13. Streubel B, Huber D, Wöhrer S, Chott A, Raderer M. Frequency of chromosomal aberrations involving MALT1 in mucosa-associated lymphoid tissue lymphoma in patients with Sjögren's syndrome. *Clin Cancer Res*. 2004;10:476-480.
14. Ye H, Liu H, Attygalle A, et al. Variable frequencies of t (11; 18) (q21; q21) in MALT lymphomas of different sites: significant association with CagA strains of H pylori in gastric MALT lymphoma. *Blood*. 2003;102:1012-1018.
15. Okabe M, Inagaki H, Ohshima K, et al. API2-MALT1 fusion defines a distinctive clinicopathologic subtype in pulmonary extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue. *Am J Pathol*. 2003;162:1113-1122.
16. Iwano M, Okazaki K, Uchida K, et al. Characteristics of gastric B-cell lymphoma of mucosa-associated lymphoid tissue type involving multiple organs. *J Gastroenterol*. 2004;39:739-746.
17. Toyoda K, Maeshima AM, Nomoto J, et al. Mucosa-associated lymphoid tissue lymphoma with t(11;18)(q21;q21) translocation: long-term follow-up results. *Ann Hematol*. 2019:1675-1687.

Reprint requests:

Kenichiro Ishibashi
Department of Maxillofacial Surgery
School of Dentistry
Aichi Gakuin University
2-11 Suemori-dori
Chikusa-ku
Nagoya 464-8651
Japan
ken1ro@dpc.agu.ac.jp