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Case report

Malignant lymphoma in the head and neck associated with benign lymphoepithelial lesion of the parotid gland☆

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Abstract

Lymphoepithelial lesion is a benign lymphoproliferative disease occasionally arises in the salivary glands, but association with malignant diseases or autoimmune diseases has also been discussed. We herein present three cases of malignant lymphoma arose in the parotid gland and the lacrimal gland, following parotid surgery for benign lymphoepithelial lesion (BLEL) of the parotid gland. Two cases had mucosa associated lymphoid tissue (MALT) lymphoma in the parotid gland; one arose in the ipsilateral parotid gland as a recurrent swelling, and the other arose in the contralateral parotid gland of the previous BLEL surgery. The third case of malignant lymphoma arose in the lacrimal gland on the ipsilateral side, and the following contralateral parotid gland remained BLEL. All three patients were female, and one patient had a past history of Sjögren's syndrome and Hashimoto's disease. All three patients were treated by chemotherapy and one patient received additional radiotherapy. To follow-up lymphoproliferative diseases in the salivary glands such as BLEL, careful observation should be made on the same gland, other major salivary glands, and other organs in the head and neck, especially in females with autoimmune diseases.

Keywords: Malignant lymphoma; Benign lymphoepithelial lesion; Mucosa associated lymphoid tissue; Parotid gland

1. Introduction

Most neoplasms that arise in the head and neck originate from epithelial tissue, but lymphoid neoplasms should also be considered as a differential diagnosis because the head and neck region has important lymph apparati such as cervical lymph nodes and Waldeyer's ring [1]. In the parotid glands, lymphoid tissue is believed to accumulate as a result of chronic inflammation of varying causes, and such lymphoid tissue has been recognized as MALT [2]. Low grade B cell malignant lymphoma associated with MALT was first described in 1983 as gastrointestinal tract lymphoma [3], but the concept has been extended to lymphomas in the lungs, thyroid glands, and salivary glands [2]. MALT lymphoma has been presumed to be associated with autoimmune diseases or inflammatory diseases [2]. BLEL is also a lymphoproliferative disease that arises in the parotid glands. BLEL had been suggested to be a benign disease since the first description of BLEL of the parotid gland in 1952 [4], however, subsequent malignancies have also been reported [5,6]. In the present study, we describe three cases of malignant lymphoma, two were diagnosed as MALT lymphoma and arose in the head and neck following parotid surgery for BLEL.

2. Case reports

2.1. Case 1

A 56-year-old woman was referred to our clinic with complaints of bilateral infraauricular swelling. She had been followed up under diagnosis of Sjögren's syndrome and Hashimoto s disease for 3 years by the Department of Internal Medicine of our university clinic. Blood examination showed positive anti SS-A

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antibody and a high titer of anti-microsomal antibody and anti-thyroglobulin antibody, which indicated high autoimmune activity. Magnetic resonance imaging (MRI) showed diffuse swelling of the bilateral parotid glands with multiple cystic changes (Fig. 1; left). Fine needle aspiration biopsy (FNAB) revealed lymphocyte aggregation with no tumor cells. After 2 years of follow up, a superficial parotid lobectomy preserving the facial nerve was performed since a multilobular hard tumor arose in the superficial lobe of the left parotid gland and the re-examined FNAB showed suspicion of MALT lymphoma. The size of the resected tumor was $38 \times 37 \times 37$ mm. No tumor was found in the deep lobe. The histological findings of the specimen showed lymphoid hyperplasia with a germinal center, atrophic salivary gland and myoepithelial islands (Fig. 2; top), and the diagnosis was BLEL. After 6 months of post-operative follow up, the right parotid gland swelling had increased. MRI was re-examined and showed growth of the right parotid tumor and recurrence of the left parotid tumor in the deep lobe (Fig. 1; right). A right superficial parotid lobectomy was performed 9 months after the first surgery. The size of the resected tumor was $40 \times 30 \times 15$ mm. The initial histopathological diagnosis of the frozen-section specimen was BLEL, but the final diagnosis was revised to MALT type malignant lymphoma. Histological findings of the specimen included severe invasion of small lymphoma cells with irregular nuclei and a pale cytoplasm into the severely atrophic salivary gland tissue with formation of LEL (Fig. 2; right). Her clinical stage was IIE of the Ann Arbor Classification [7]. No bone marrow involvement was observed by bone marrow biopsy specimen. Blood examination showed slightly high LDH titer (466 IU/l), leukocytopenia ($1990/mm^3$) and anemia ($339 \times 10^4/mm^3$). Her performance status at the diagnosis of malignant lymphoma was 0. She was referred back to the Department of Internal Medicine for the treatment of malignant lymphoma. Since initial parotid lesion was multiple, multidrug chemotherapy was planned. After three courses of THP-COP (pirarubicin hydrochloride-cyclophosphamide, vincristine, and prednisolone) chemotherapy, remnant lesion was pointed out by computed tomography (CT), and 45.6 Gy of irradiation was performed. She has been followed up for 1 and a half years without recurrence of the tumor, from both otolaryngological and hematological viewpoints.

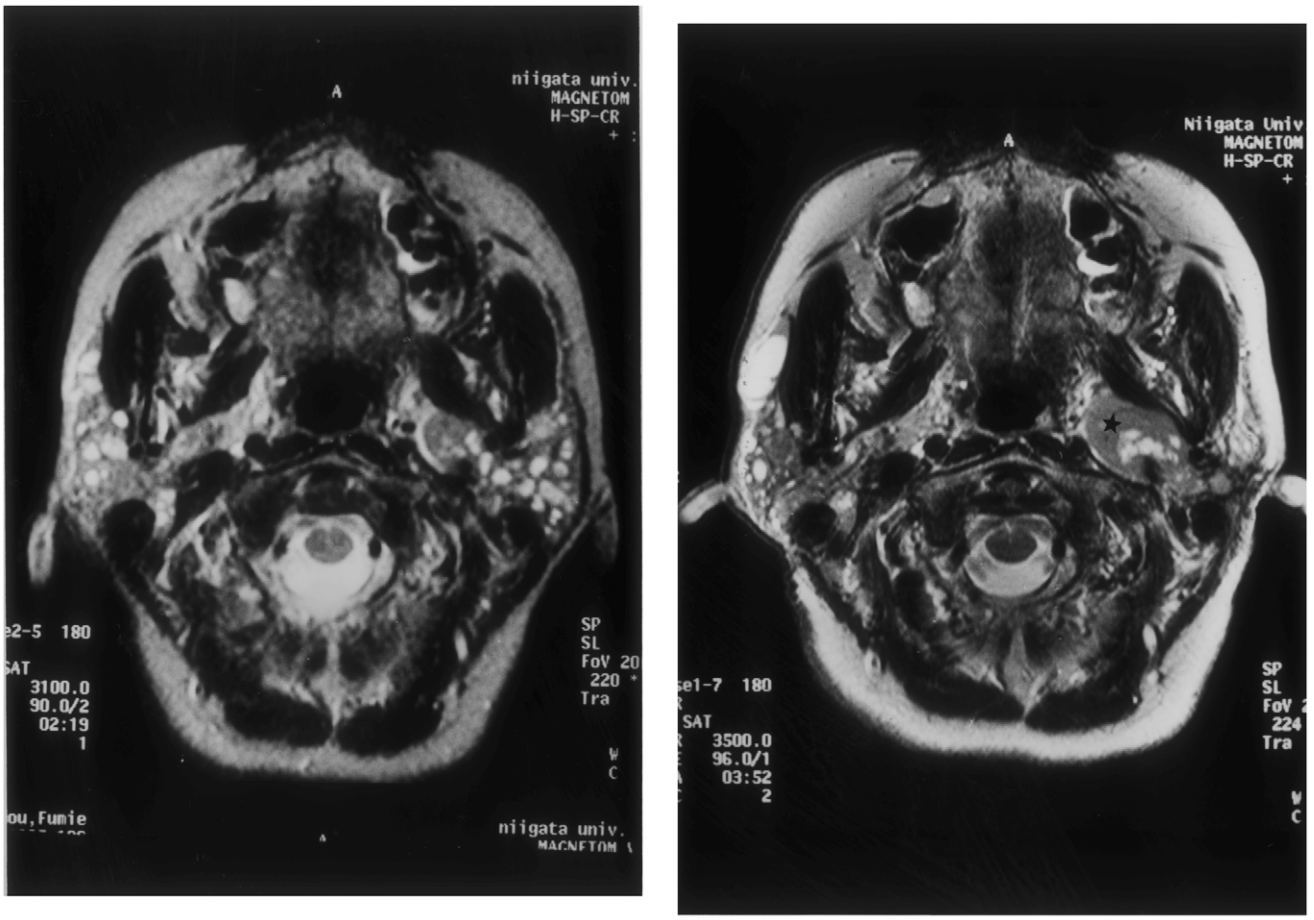

Fig. 1. Left: MRI of the Case 1 taken before the first surgery. Bilateral parotid glands were swollen with multiple cystic changes. Right: MRI of the Case 1 taken 5 months after the first surgery. Growth of right parotid gland swelling with multiple cysts and recurrence of left parotid gland tumor in the deep lobe (*) were seen.

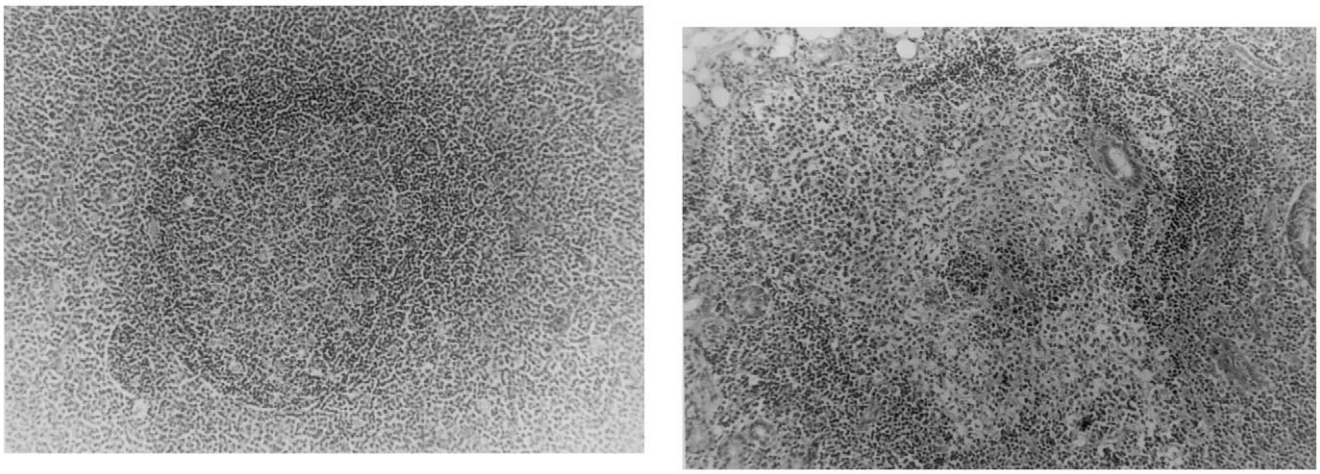

Fig. 2. Left: Histopathological findings of left parotid tumor (first surgery) of the Case 1. Lymphoid hyperplasia with germinal center was seen with atrophic salivary gland tissue and myoepithelial islands. Right: Histopathological findings of right parotid tumor (second surgery) of the Case 1. Severe invasion of small lymphoma cells with irregular nucleus with pale cytoplasm into the severely atrophic salivary gland tissue, with formation of LEL was seen.

2.2. Case 2

A 77-year-old woman was referred to our clinic with complaints of a right infraauricular hard swelling. CT showed a solid mass with irregular surface in the right parotid gland (Fig. 3; left). No abnormal findings were shown on blood examination. Since the radiological diagnosis suggested a malignant parotid tumor, a superficial parotid lobectomy was performed 1 month after the first visit. The size of the resected tumor in the superficial lobe was $35 \times 35 \times 35$ mm, and another tumor ($15 \times 15 \times 15$ mm) found in the deep lobe was also resected with surrounding parotid gland tissue. The facial nerve was preserved. The histological finding included replacement of the gland structure by lymphoid cells and epithelial hyperplasia of salivary ducts, and the diagnosis was BLEL. Post-operative follow up was conducted by the regional clinic from which the patient was referred. Five years after the first surgery, a right retroauricular swelling appeared. MRI showed a mass lesion in the right pre-retroauricular region with lymph nodes swelling in the right jugular chain (Fig. 3; right). Since the clinical and radiological findings indicated suspicion of malignant lymphoma, an open biopsy of the right retroauricular tumor was performed. The tumor was white, hard and adhered to the surrounding tissue. The histological findings included severe invasion of lymphoma cells into the connective tissue, and the diagnosis was MALT type malignant lymphoma. Her clinical stage was IE of the Ann Arbor Classification [7]. No bone marrow involvement was observed. Blood examination showed high LDH titer (531 IU/l) and normal blood cell counts. Her performance status at the diagnosis of malignant lymphoma was 0. Since the patient rejected additional surgery and irradiation, chemotherapy was planned. According to the patient's wishes, she was referred to the regional clinic and was treated with two courses of THP-COP chemotherapy. She has been followed up by the Departments of Otolaryngology and Internal Medicine of the clinic with a partially decreased tumor for 4 years after the diagnosis of malignant lymphoma.

2.3. Case 3

A 64-year-old woman was referred to our clinic with complaint of multiple left infraauricular hard swellings. She also had a small swelling in the right parotid gland. CT showed strongly enhanced tumors in the left parotid gland. FNAB was not performed because heavy bleeding after FNAB was predicted by the strong enhancement of CT. A left superficial parotid lobectomy preserving the facial nerve was performed 4 months after the first visit. Three round tumors ($25 \times 25 \times 25$ mm, $15 \times 15 \times 15$ mm, $10 \times 8 \times 8$ mm) were resected. Histopathological finding showed small lymphocyte aggregation with myoepithelial islands and atrophic salivary gland tissue, and the diagnosis was BLEL. Eighteen months after the first surgery, swelling of the left eyelid appeared. CT showed a tumor in the left lacrimal gland (Fig. 4; left). An open biopsy of the lacrimal gland tumor was performed at the Department of Ophthalmology of our university clinic 2 years after the first parotid surgery. The specimen showed diffuse aggregation of small lymphoma cells, and the histopathological diagnosis was malignant lymphoma (small lymphocytic lymphoma). Since growth of the right parotid swelling appeared 1 month after the diagnosis of lacrimal gland malignant lymphoma, and malignant lymphoma involvement to the right parotid gland was suspected (Fig. 4; right), a subtotal removal of the right parotid gland swelling preserving the facial nerve was

carried out for the histological diagnosis, but the histopathological diagnosis was also BLEL. Her clinical stage was IE of the Ann Arbor Classification [7]. No bone marrow involvement was observed. Blood examination showed slightly high LDH titer (457 IU/l) and normal blood cell counts. Blood examination also showed positive anti SS-A antibody, although histological diagnosis of the lip minor salivary gland biopsy was not Sjögren's syndrome. Her performance status at the diagnosis of malignant lymphoma was 0. Since complete resection and irradiation were difficult due to the expected complication of the eye, chemotherapy was performed. The patient was treated with six courses of COP chemotherapy for the malignant lymphoma of the lacrimal gland at the Department of Internal Medicine of our university clinic, and a complete response was obtained without recurrence of the lymphoma for 8 years. Eight years after the treatment, a swollen cervical lymph node appeared and was resected for histological diagnosis. The specimen showed similar findings as the lacrimal gland lesion, and the diagnosis was recurrence of the malignant lymphoma. The cervical node was solitary and completely resected. No recurrence has been seen for 2 years after the additional courses of COP therapy.

3. Discussion

Various epithelial tumors arise in the parotid gland, but lymphoproliferative diseases must also be considered in the differential diagnosis of parotid tumors, because the parotid gland has a rich lymphatic network [8]. Malignant lymphomas of the parotid gland are rare, and the incidences were reported to be 1.7% [9], 4.0% [10], and 5% [11] of total parotid tumors. In the malignant lymphomas of the salivary glands, there are two disease statuses; part of a disseminated process or as the first clinicopathologic evidence of lymphoma [12]. The primary salivary gland lymphoma were reported as only 6 of 324 lymphomas in the parotid gland [12]. In our department, 101 parotid surgeries were performed under the diagnoses of parotid tumor between 1996 and 1999. In those parotid tumors, 76 (75%) were benign and 25 (25%) were malignant, and only 5 (5%) were malignant lymphoma.

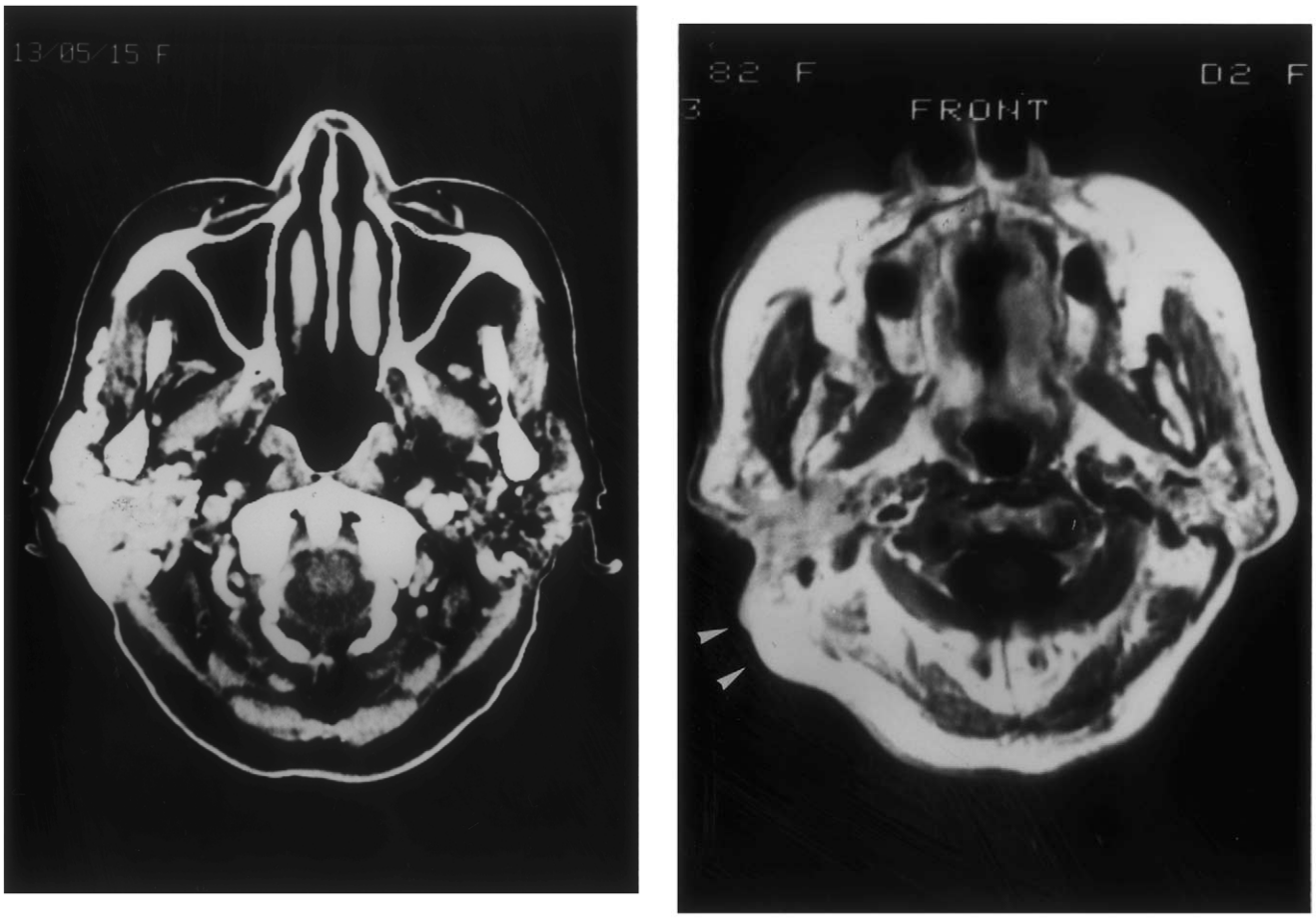

Fig. 3. Left: CT of the Case 2 taken before the first surgery. A $30 \times 30 \times 20$ mm^3 solid mass with irregular surface located in both superficial and deep lobe of right parotid gland. Right: MRI of the Case 2 taken 5 years after the first surgery. The mass lesion spread from post-parotidectomy region to retroauricular region without image of remnant parotid gland tissue (arrowheads).

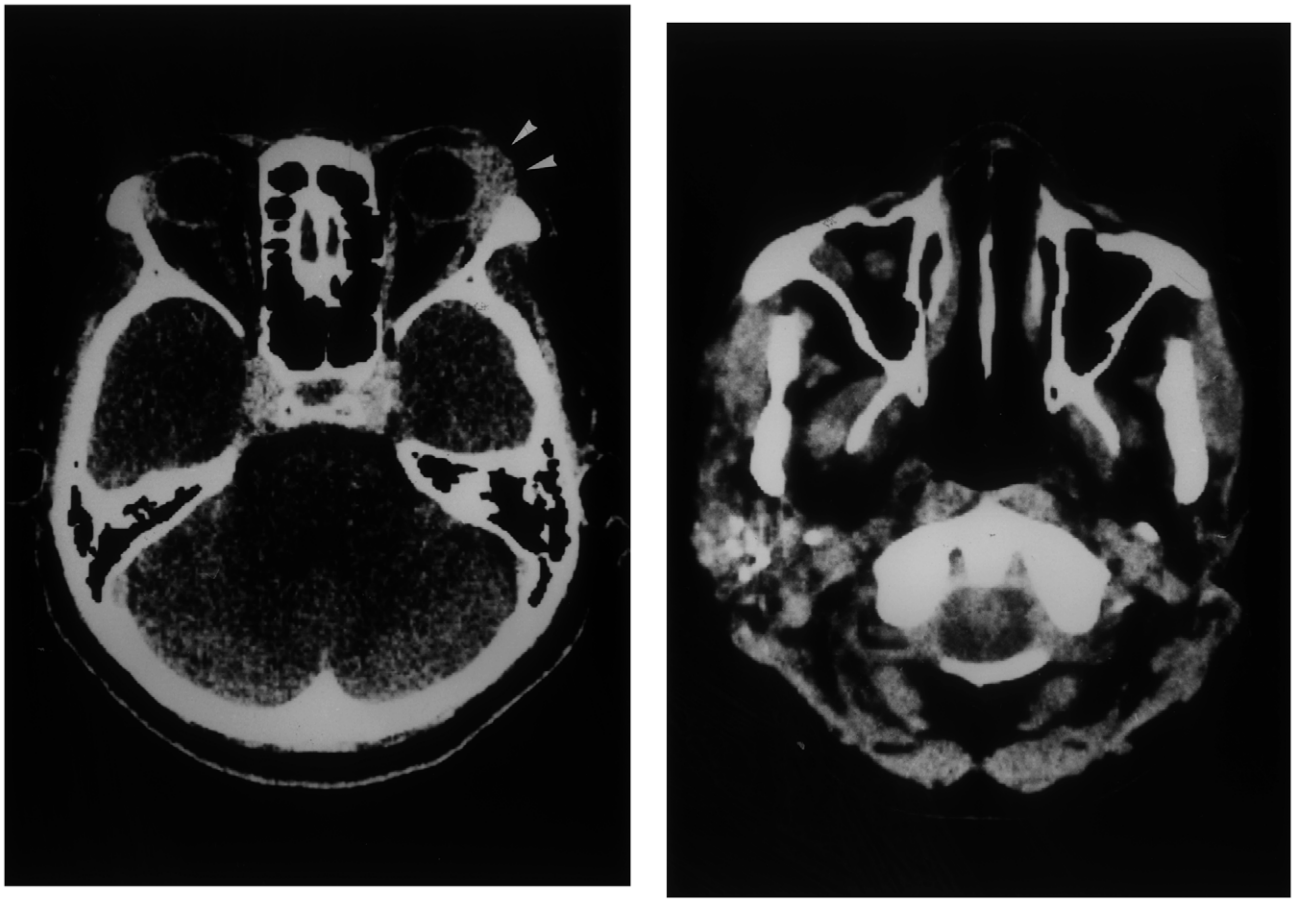

Fig. 4. CT taken 2 years after the left parotid surgery and 6 months before the surgery of left lacrimal gland of the Case 3. Left: Swelling of left lacrimal gland with high CT density was seen (arrowheads). Right: Diffuse swelling of right parotid gland with multiple calcification was seen. (Left parotidectomy had been done.)

The concept of BLEL was originally proposed as a parotid gland disease and was distinguished from other inflammatory diseases or benign tumors of the parotid gland [4]. Histopathological features of BLEL include aggregation of lymphoid tissue with a germinal center associated with atrophy of the acinar parenchyma and ductal changes described as myoepithelial islands [4,6]. BLEL is a benign disease but multiple organ involvement may occur [6]. Resection preserving the facial nerve or additional radiotherapy for residual or recurrent tumors have been recommended for the treatment of BLEL [4–6].

The concept of MALT lymphoma was established in the past two decades [2,3], and is classified as marginal zone B-cell lymphoma in the Revised European–American Classification of Lymphoid Neoplasms (REAL) [13], and World Health Organization Classification of Neoplastic Diseases of the Hematopoietic and Lymphoid Tissues [14,15]. MALT lymphoma is characterized as a type of low-grade extranodal B-cell lymphoma, and its histopathology consists of B cells surrounding the follicles and selectively infiltrating the epithelium to form the characteristic LEL [2]. Characteristic MALT lymphoma cells are small to medium sized with a moderate amount of cytoplasm, which is sometimes pale staining, and shows a nucleus with an irregular outline resembling that of centrocytes (small cleaved cells) [2], which were seen in the specimen of the right parotid tumor of Case 1 (Fig. 2; bottom). Malignant lymphoma in the lacrimal gland of Case 3 was not characterized as MALT lymphoma histologically. However, malignant lymphomas involving the lacrimal glands are generally similar to salivary MALT lymphoma except that LEL are not so numerous or well developed [2].

The relationship between malignant lymphoma and BLEL has been discussed histologically as juxtapositioning of LEL in malignant lymphoma specimens [16], and MALT lymphomas are believed to arise from BLEL, not from normal intraparotid lymphoid aggregates [17].

Associations between malignant lymphoma and autoimmune diseases such as Sjögren's syndrome, systemic lupus erythematosus, Hashimoto's disease [2,8,10,11,17] or inflammatory diseases such as *Helicobacter pylori* infection in the stomach [2] have been

discussed, although no gastric lesions were observed by stomach examination in the present three cases. The incidence of malignant lymphoma in Sjögren's syndrome patients was reported to be 44-fold higher than in overall patients [18]. The interval between the onset of Sjögren's syndrome and the development of malignant lymphoma can be extend over years [18].

Treatment for MALT lymphoma is not fully established since the concept of the disease has only recently been proposed, but surgery or local radiotherapy for localized MALT lymphoma and chlorambucil for advanced disease were recommended [19]. Eradication of *H. pylori* is also a recommended therapeutic modality for gastric MALT lymphoma [20].

In the patients reported here, all showed multiple, multilobular, or irregular-surfaced hard mass in the parotid gland which were different from those of typical benign parotid tumors such as pleomorphic adenoma or Warthin's tumor. However, the differential diagnosis of malignant lymphoma or other parotid tumors from the clinical findings (e.g. inspection, palpation, radiological findings) was not possible. All three patients in the present study could not be diagnosed as malignant lymphoma before the first parotid surgery. Case 1 had a history of Sjögren's syndrome and Hashimoto s disease, and Case 3 had positive anti SS-A antibody on blood examination, although histological findings of Sjögren's syndrome were not observed. In Case 2, malignant lymphoma developed in the same parotid gland of the previous BLEL. Development of malignant lymphoma occurred in the contralateral parotid gland of the previous BLEL in Case 1. In addition, malignant lymphoma arose in the lacrimal gland in Case 3. Intervals between the diagnoses of BLEL and malignant lymphoma of the three patients in the present study were 9 months, 5 years, and 2 years, respectively.

High incidence of malignant lymphoma in patients with autoimmune diseases has been repeatedly emphasized [8,10,11,16], and Case 1 of this paper had histories of Sjögren's syndrome and Hashimoto s disease, and Case 3 had positive anti SS-A antibody. All three patients in the present study were female. Surgery was strongly recommended as a diagnostic tool of malignant lymphoma of the parotid gland [10], since histological evaluation is essential for treatment of malignant lymphoma. For the present patients, the recommendation for parotid surgery and careful follow-up based on unusual clinical findings might have led to the diagnosis of malignant lymphoma by histology of the resected specimens. Therefore, in the treatment and follow up of the patients with parotid swelling, parotid surgery is positively recommended both in order to treat the tumor and to ensure histological diagnosis of the tumor for further follow up planning. When the parotid tumor is histopathologically diagnosed as lymphoploriferative disease, careful long-time follow up is needed with attention to the same gland, other major salivary glands, or other organs in the head and neck, especially in female patients with autoimmune diseases or chronic inflammatory diseases.

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