

Concurrent Presence of Sjogren's Syndrome, Warthin Tumor, and MALT Lymphoma in a Parotid Gland and Hashimoto's Thyroiditis

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A 54-year-old female patient was referred due to a mass in the left salivary gland. A neck CT was performed and surgery was agreed due to a suspected Warthin tumor. The patient was also diagnosed with Sjogren's syndrome and Hashimoto's thyroiditis and treated. Warthin tumor and extranodal marginal zone B-cell lymphoma were also diagnosed after parotidectomy. The coexistence of the two autoimmune diseases, Hashimoto's thyroiditis and Sjogren's syndrome, has been reported, as has the coexistence of Warthin tumor and malignant tumor within a single salivary gland. However, these four diseases have not previously been reported in an individual patient. The authors treated a patient who was first diagnosed with Sjogren's syndrome and Hashimoto's thyroiditis, and subsequently also with Warthin tumor and extranodal marginal zone B-cell lymphoma after superficial parotidectomy. Therefore, this case is reported together with a related literature review.

Key Words: Hashimoto's thyroiditis, Sjogren's syndrome, Warthin tumor, MALT lymphoma

Introduction

The autoimmune disease Sjogren's syndrome often affects organs other than exocrine glands, these extraglandular manifestations being observed in 25% of patients with the primary Sjogren's syndrome. Organs affected by Sjogren's syndrome include the thyroid, lymph nodes, bone marrow, skin, lung, heart, kidneys, and brain. Sjogren's syndrome accompanied by thyroid diseases has been reported with frequencies between 10–70% and Sjogren's syndrome accompanied by Hashimoto's thyroiditis is also commonly observed. Malignant lymphomas may develop when Sjogren's syndrome affects bone marrow or lymph

nodes, and the development of non-Hodgkin's lymphoma was reported in 2.5% of patients with primary Sjogren's syndrome.^{1–3)} In addition, Sjogren's syndrome accompanied by Warthin tumor in salivary glands or by malignant lymphomas in the lymph nodes of salivary glands has been reported in 20 patients. The pathogenesis of these conditions is, however, not clearly understood.⁴⁾

Therefore, the authors present the case of a 56-year-old female patient who was primarily diagnosed with Hashimoto's thyroiditis and primary Sjogren's syndrome, and additionally diagnosed with Warthin tumor in the salivary glands and marginal zone B-cell lymphoma by surgical biopsy, after referral to the hospital because of a mass in the salivary glands.

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Case Report

A 56-year-old female patient was referred due to a mass in the left parotid gland which had detected a month prior to the appointment. The patient stated that she had suffered from dry mouth and dry eyes for several years but there was no other medical history. On admission, she did not indicate dysphasia or odynophagia, her vital signs were all within the normal ranges, and she was afebrile. On physical examination, the gross measurement of the mass was approximately 2 cm, and appeared to be solid and mobile. There was no tenderness, redness, or localized warmth. The oral cavity appeared normal and healthy, as did the pharyngolaryngeal area on visual inspection with a laryngoscope.

Peripheral blood test results showed the white blood cell count $5430/\text{mm}^3$, neutrophils 82.7%, hemoglobin 13.5 g/dL, platelets $246,000/\text{mm}^3$, blood urea nitrogen 12.6 mg/dL, creatinine 0.78 mg/dL, and glucose 95 mg/dL. The liver function test showed that alkaline phosphatase, alanine transaminase, and aspartate transaminase were 70 U/L, 24 U/L, and 14 U/L, respectively. Electrolytes were within the normal ranges with values of sodium 149.4 mM, chloride 115.5 mM, and potassium 4.6 mM. The total cholesterol level was increased to 235 mg/dL. Multiple masses in both parotid glands with internal cystic changes and focal calcification were shown by neck computed tomography (CT) (Fig. 1). Only multiple benign looking lymphocytes and no malignant cells were found by a

needle aspiration biopsy of the left parotid gland.

No corneal erosion was noted when testing for xeroma, however, lacrimal hyposecretion was revealed by a Shirmer test. Hyposalivation was found in a salivary gland scan for xerostomia. Blood tests for Sjogren's syndrome indicated a positive speckled pattern of antinuclear antibody (1 : 640) and positive anti-Ro(ssA)/La(ssB) antibody (1 : 325 and 1 : 656). Anti-ds-DNA antibody, C3, and C4 were within their normal ranges, with values of 4.55 IU/mL, 101 mg/dL, and 23 mg/dL, respectively. The patient did not have proteinuria. Hypothyroidism was revealed by a thyroid function test, as indicated by thyroid-stimulating hormone (TSH) 27.5 mIU/L (0.27–4.2 mIU/L), free T4 0.66 ng/dL (0.93–1.70 ng/dL), and T3 128.8 ng/dL (80–200). Anti-thyroglobulin antibody was > 4000 IU/mL and anti-thyroid peroxidase antibody was significantly increased above 600 IU/mL, whereas the TSH receptor antibody was negative. The patient was diagnosed with Sjogren's syndrome based on the clinical symptoms (xeroma and xerostomia), the results of the Shirmer test (lacrimal hyposecretion), a salivary gland scan (hyposalivation), and the positive results for anti-Ro(ssA)/La(ssB) antibody. She was additionally diagnosed with hypothyroidism secondary to Hashimoto's thyroiditis based on the blood test results, which were positive for thyroid autoantibodies. Hydroxychloroquine 400 mg/day and levothyroxine sodium 100 μg /day were prescribed for a month to treat the Sjogren's syndrome and Hashimoto's thyroiditis. Consequently, xeroma and xerostomia improved and free T4 increased to 1.44 ng/dL, which was within the normal range.

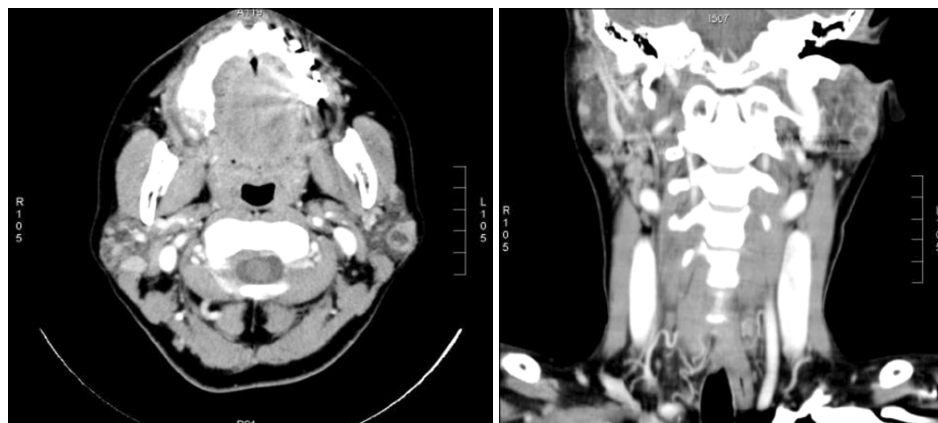


Fig. 1. Neck CT scan shows multiple masses with internal cystic changes and focal calcification in both parotid glands.

Superficial parotidectomy was performed to remove the mass in the left parotid gland. On gross examination, the salivary gland measured $4.5 \times 3.7 \times 1.7$ cm and there was a gray-colored mass of 1.7×1.9 cm in this gland. Microscopic examination revealed benign proliferation of the glandular epithelium surrounded by extensive proliferation and infiltration of atypical lymphocytes, which suggested a mixed tumor of Warthin tumor and malignant lymphoma (Fig. 2). Immunohistochemical staining revealed cytokeratin-positive cells in lymphoepithelial lesions. A small number of scattered CD 3-positive cells were observed while the majority of cells were CD 20 positive. The atypical lymphocytes showed bcl 2-positive, bcl 6-negative, and Ki-67-positive in 5–20% that suggested an extranodal mar-

ginal zone B cell lymphoma. To determine the stage of the extranodal marginal zone B cell lymphoma, bone marrow exam, endoscopy, chest and abdominal CT, and [18F]-fluorodeoxyglucose positron emission tomography/CT (18-FDG PET/CT) were performed. PET/CT image shows a focal hot lesion on a right neck level II node and right parotid area (Fig. 3). These investigations confirmed that there was no metastasis other than the lesions in both parotid glands, indicating non-Hodgkin's lymphoma of Ann Arbor stage VI. The patient received six cycles of chemotherapy with rituximab, cyclophosphamide, vincristine, and prednisone after surgery. She is currently undergoing chemotherapy with rituximab alone.

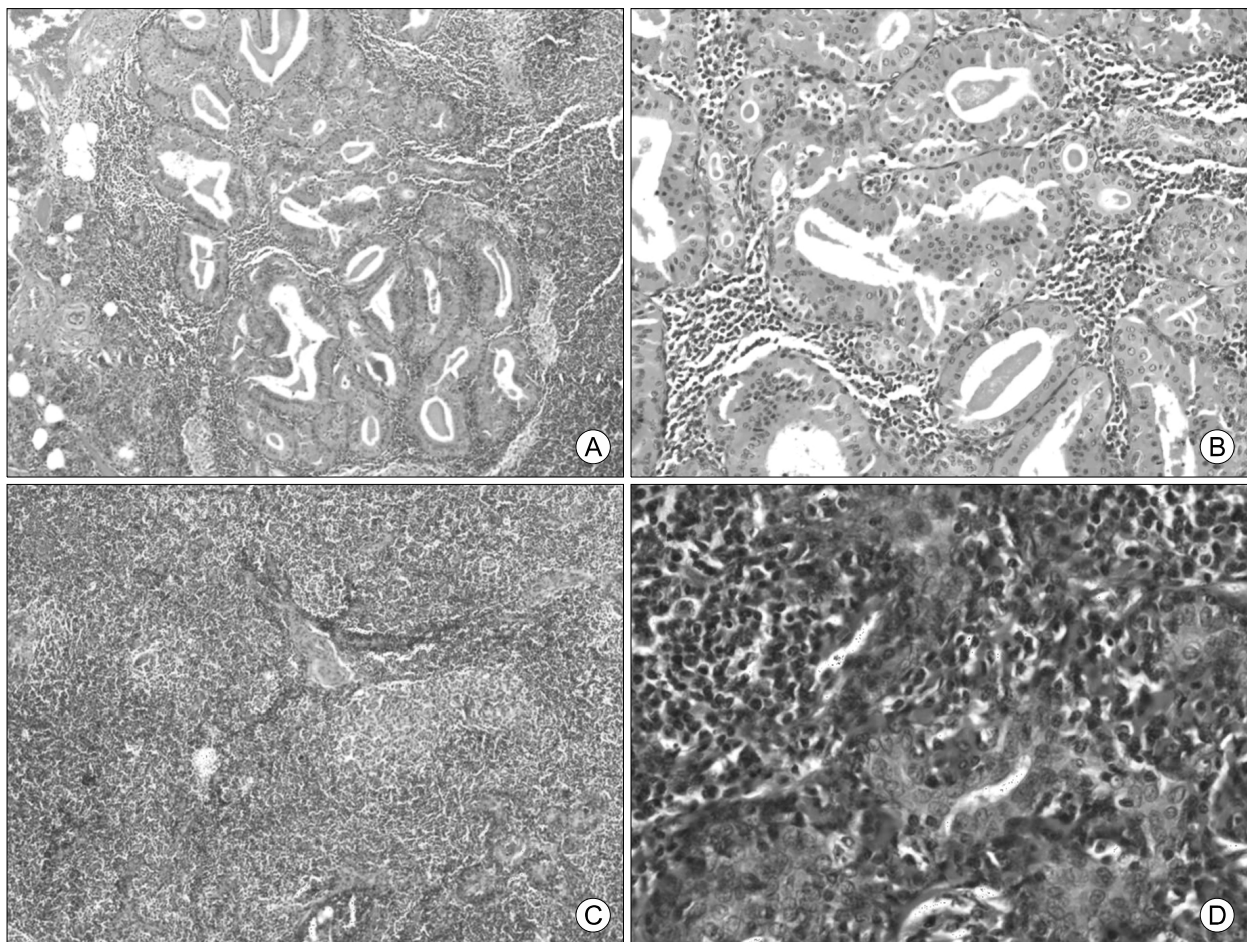


Fig. 2. Microscopic findings. (A, B) Warthin tumor. The tumor is composed of a mixture of ductal epithelium and a lymphoid stroma (H&E stain, $\times 40$, $\times 100$). (C, D) MALT lymphoma. (C) Histological examination of surgical specimens shows diffuse proliferation of atypical small lymphocytes in the mucosa and submucosal layer (H&E stain, $\times 40$). (D) Infiltrative lymphocytes are seen within the glandular epithelium (lymphoepithelial lesion) and the gland structures are disrupted in a high power field (H&E stain, $\times 200$).

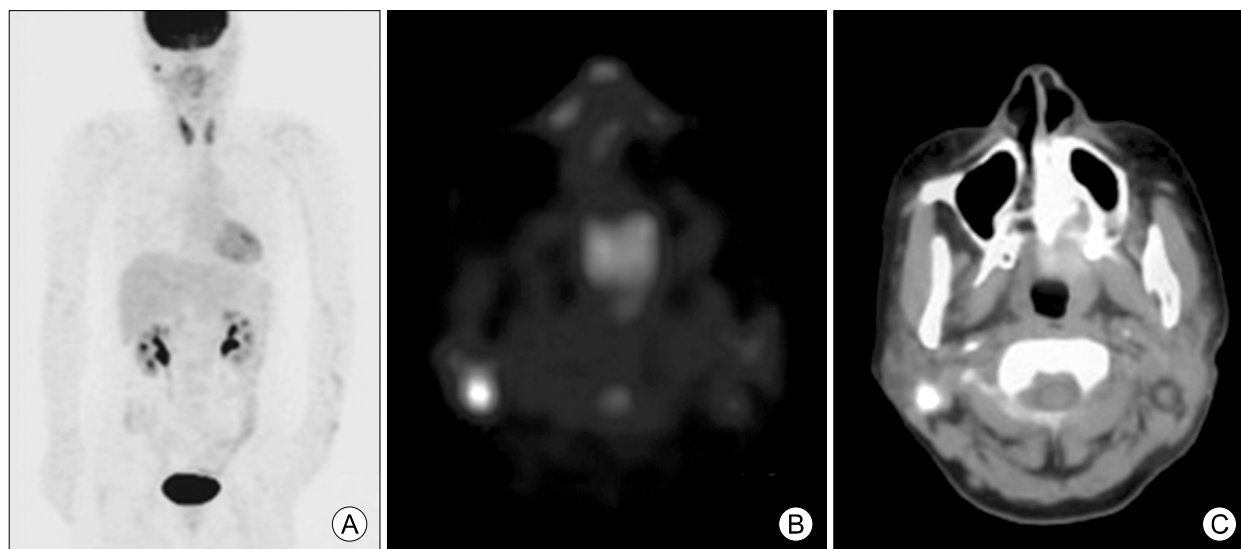


Fig. 3. (A) Coronal PET image shows a focal hot lesion on a right neck level II node and an incidental finding of thyroiditis. (B, C) Transaxial PET and fused PET/CT images show a hypermetabolic lesion on right parotid area (SUVmax=5.94).

Discussion

Sjogren's syndrome causes chronic inflammation in salivary and lacrimal glands, leading to hyposecretion. Primary Sjogren's syndrome is when this condition occurs independently, whereas secondary Sjogren's syndrome develops in association with other diseases. Extraglandular manifestations can occur within 7.5 years after the onset of primary Sjogren's syndrome, being reported in 25% of such patients, with non-Hodgkin's lymphoma in 2.5% of the cases.⁵⁾ Other autoimmune diseases were reported in 33% of patients with Sjogren's syndrome.²⁾

The prevalence of Sjogren's syndrome accompanied by thyroid diseases ranges from 10–70%. Hypothyroidism is more closely associated with Sjogren's syndrome than hyperthyroidism. Sjogren's syndrome accompanied by Hashimoto's thyroiditis, an autoimmune disease, is also commonly reported. Of these cases, anti-peroxidase antibody was detected in 18% and anti-thyroglobulin antibody in 13%. Hypothyroidism is the most common of the autoimmune diseases accompanied by Sjogren's syndrome according to a retrospective study conducted by Lazarus et al.²⁾ In contrast, Ramos-Casals et al.⁶⁾ reported that there was no statistically significant difference in the preva-

lence of thyroid diseases between the Sjogren's syndrome patient group and the age- and sex-matched control group because thyroid diseases were prevalent among young females.

Lymphoid malignancy may occur among patients with long-term Sjogren's syndrome. This malignancy develops because Sjogren's syndrome activates polyclonal B cells, and lymphocytes infiltrate the exocrine glands.⁷⁾ The morbidity rate of non-Hodgkin's lymphoma among patients with Sjogren's syndrome is reported at 5%, representing 16–44 times higher than the general population.⁸⁾ Its risk factors include positive anti-Ro/SSA and anti-La/SSB antibodies, hepatitis C virus, peripheral neuritis, and positive rheumatoid factor. Lymphoid malignancy was expressed as extranodal marginal zone B-cell lymphoma (MALT lymphoma) in 44% of cases, as diffuse large B cell lymphoma (DLBL) in 24% of cases, and as follicular center cell lymphoma in 24% of cases.⁹⁾

Lymphoma in salivary glands is rarely accompanied by Warthin tumor, a benign tumor in salivary glands. The hypothesis describing the lymphoma as originating from the stroma of the Warthin tumor is considered the most convincing. However, others have suggested that salivary gland lymphoma accompanied by Warthin tumor may have originated from cervical lymph nodes. Twenty cases of salivary gland lymphoma accom-

panied by Warthin tumor were reported up to 2005. These included 10 cases of follicular lymphoma, diffuse large B cell lymphoma, diffuse mixed small and large cell lymphoma, and small lymphocytic lymphoma. It is widely thought that antigen stimulation of the Warthin tumor is responsible for the onset of lymphoma.⁴⁾

The patient in this case report was referred due to a salivary mass and was diagnosed with Warthin tumor in the salivary glands and extranodal marginal zone B-cell lymphoma after surgery as well as with Hashimoto's thyroiditis and Sjogren's syndrome. The patient was at risk of developing malignant lymphoma accompanied by Sjogren's syndrome as she was positive for the anti-Ro/SSA and anti-La/SSB antibodies. She was also at risk for autoimmune thyroiditis, being positive for the anti-thyroglobulin and anti-TPO antibodies. However, there is a lack of research evidence to explain why the associated diseases occur in relationship to these antibodies and the theoretical pathogenesis of this coexistence is not yet fully understood.

The authors found the concurrent presence of Sjogren's syndrome, Hashimoto's thyroiditis, extranodal marginal zone B-cell lymphoma, and Warthin tumor in the salivary glands of a patient. This case is considered to be significant because it is the first reported example of the coexistence of these four diseases. Although theoretical evidence is currently

lacking, it is expected that its pathogenesis will become clear through further case reports and research.

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