

Submandibular Gland MALT Lymphoma Associated With Sjögren's Syndrome: Case Report

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Lymphoma is a common disease of the head and neck. Mucosal-associated lymphoid tissue (MALT) lymphoma constitutes a rare type of extranodal lymphoma. The Waldeyer's ring is one of the most common sites of occurrence, but MALT lymphoma may also arise in salivary glands, lung, stomach, or lacrimal glands. In the oral cavity, it may be confused with swellings from dental infection or sinus inflammation. Often, the patient will seek a dentist because of mobile teeth or because a denture no longer fits. We report a case of a female patient with salivary gland dysfunction and pain of several years' duration, who, after numerous tests and hospitalizations, was diagnosed with Sjögren's syndrome. She later developed mucosal-associated lymphoid tissue lymphoma. We discuss the diagnosis, treatment, and prognosis of this entity. MALT lymphoma is rare in salivary glands. In primary-Sjögren's syndrome, predisposition of the patient for development of malignant non-Hodgkin's lymphoma (4% to 10%) is well established. In this case, long-standing sialadenitis and Sjögren's syndrome seem to be the etiological factors. In cases of chronic infection of salivary glands and the presence of autoimmune syndromes, MALT lymphoma should be considered in the differential diagnosis. Consults should be called to ophthalmology, rheumatology, and head and neck oncologists for proper workup, staging, and treatment.

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Lymphoma is a common malignancy of the head and neck. Approximately one fourth of head and neck lymphomas are extranodal.¹ Mucosa-associated lymphoid tissue (MALT) lymphomas constitute extranodal presentation of a low-grade B-cell lymphoma, and the Waldeyer's ring is one of the most common

sites of occurrence. MALT lymphoma may also arise in salivary glands, lung, stomach, or lacrimal glands. In the oral cavity, they present as nonulcerated, diffuse, fleshy enlargements that may be confused with swellings from dental infection or sinus inflammation. Often individuals presenting with lymphomas seek a dentist because of mobile teeth or because the denture no longer fits.²

MALT lymphoma is commonly associated with pre-existing autoimmune diseases such as long-standing Sjögren's syndrome (SS)³ or with chronic immune stimulation such as *Helicobacter pylori* infection.

It has been shown that 4% to 10% of the patients suffering from SS develop lymphomas, and 80% of these lymphomas are in the form of MALT lymphoma.^{4,5} MALT-type lymphomas are the most common lymphomas associated with the salivary glands.² The parotid gland is usually involved, followed by the submandibular gland, which commonly presents as a painless enlargement. Some cases are bilateral, and some show multiple involvement.

MALT lymphoma has a slow progression of spread from the primary site, and therefore early stages are usually localized. However, dissemination to other sites is not uncommon, and it is reported to be as high

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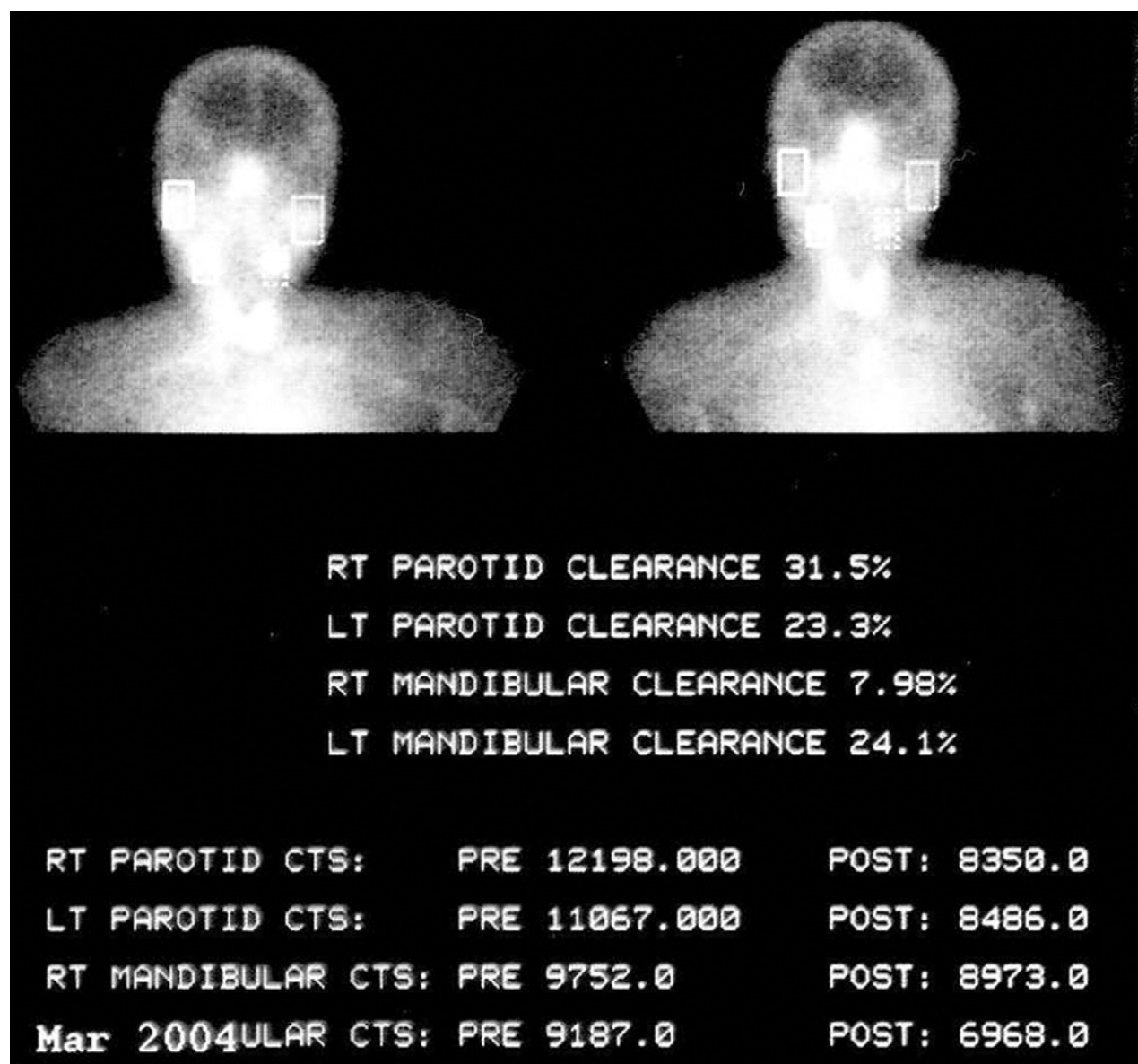


FIGURE 1. Initial nuclear study revealing depressed activity of salivary glands.

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as 25%.^{6,7} In the stomach, MALT lymphoma is multifocal and has a higher rate of recurrence status postexcision. Most cases of MALT lymphoma involving the head and neck present with no ulcerated and nonpainful enlargement of the posterior hard and soft palate and some times with lymphadenopathy. The definitive diagnosis is based on detailed histological evaluation of the entire specimen.

Histologically, MALT-type lymphomas show small to intermediate-size B cells, occasionally transformed blasts, and plasma cells. Low-grade MALT lymphoma has a cytogenetic feature consistent with the t(11;18)(q21; q21) or t(14;18)(q32; q21) Bcl-2 translocation.⁸

Most patients with MALT lymphoma have a favorable outcome, with an overall 5-year survival rate of 100% for disease of the intestines, lungs, breasts, thyroid, and skin. The 5-year survival is lowered to 46% for the upper airway tract. Salivary glands with MALT lymphoma have a 5-year survival rate of 97% with radiation or chemotherapy, with or without immunotherapy. As an immunotherapy option, rituximab, a monoclonal antibody against CD20, has been reported as a viable option in literature as a sole treatment for MALT-type lymphoma, exclusive to salivary glands.⁹ Average bone marrow involvement of 9% has been identified for MALT-type salivary gland lymphomas.¹⁰



FIGURE 2. Axial views of neck computed tomography scan showing enlarged right salivary gland and bilateral lymph nodes.

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The submandibular triangle is the housing to the submandibular gland and a portion of the parotid gland. The submandibular triangle is a site prone to hematologic malignancies, including various forms of leukemia and lymphoma. These malignancies appear in the form of nodal or salivary gland enlargements and can be bimanually palpated during an examination. As reported in the literature, only 5% to 10% of non-Hodgkin lymphomas are located in the salivary glands¹¹ and represent 1.7% of all reported salivary neoplasms.¹²

Case Report

A 35-year old Hispanic female presented to our outpatient clinic with a chief complaint of right submandibular pain. No contributory medical history, no known allergies, and no medications were identified. Upon extraoral examination, a soft and fluctuant swelling of the right submandibular area was noted. Low salivary flow was detected during intraoral examination. Clinical examination and computed tomography (CT) scan ruled out sialoliths and odontogenic sources of the condition. A tentative diagnosis of perforated sialadenitis of the right submandibular gland was made.

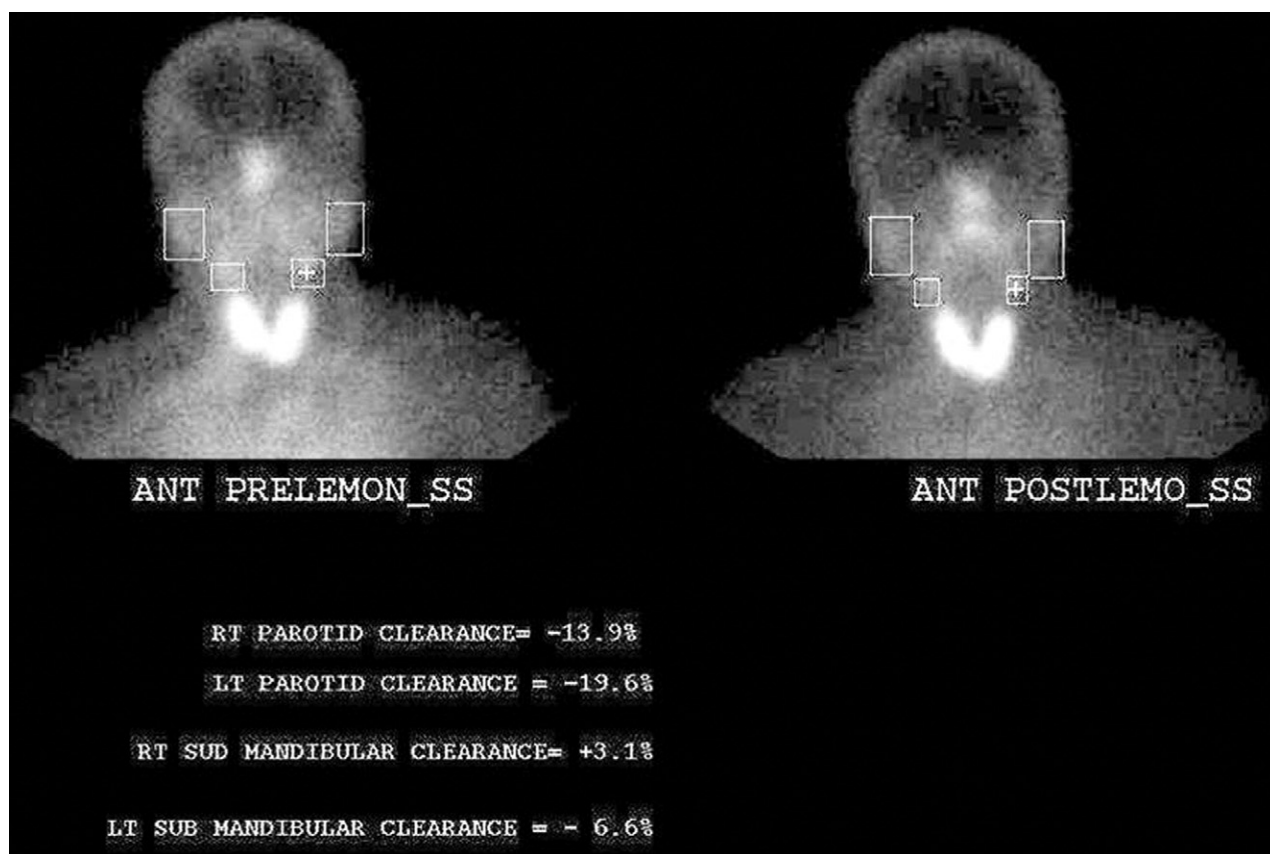


FIGURE 3. Nuclear study revealing severely depressed activity of all glands.

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FIGURE 4. Surgical specimen of right submandibular gland.

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Under general anesthesia using an extra oral approach, surgical incision and drainage was performed and treatment with intravenous antibiotics was initiated. The patient failed to follow up.

One year later, the patient presented to our clinic again with similar symptoms, excluding the fluctuant nature of the area. On physical examination, an extremely firm and tender right submandibular gland was noted. There was xerostomia but no dry eyes. The patient was admitted and managed with hydration and intravenous antibiotics. During this visit, dynamic scintigraphy, with prelemon and postlemon test showed low activity of all glands. The clearance values were 31.5% and 23.3% for right and left parotids and 7.98% and 24.1% for right and left submandibular glands (Fig 1).

To rule out SS, a lip biopsy was also done. With the focus score (number of lymphocytic foci adjacent to normal appearing acini, containing more than 50 lymphocytes per 4 mm² of glandular tissue) of greater than 1, SS was considered. The patient declined further studies and treatment.

Five years later, the patient presented to the emergency department complaining of similar symptoms as previous visits. She had a swollen right submandibular gland, severe pain, and low salivary flow. The patient also reported having had multiple other similar occurrences during the past years, treated by her primary physician with pain management and oral antibiotics. The laboratory values were significant for elevated white blood cell level of 12.6 k/cm.

A CT scan of the neck revealed mildly enlarged nodes distal to the right and left submandibular glands (Fig 2). The right submandibular gland was considered slightly enlarged. At this time, the patient was treated with hydration, pain management, and intravenous antibiotics and was discharged after 4 days. A new dynamic scintigraphy showed that her salivary glands were functioning below average. The report for salivary glands clearance was lowest for the parotid glands (-13.9% to -19.6%) and highest for the symptomatic right submandibular gland (+3.1%). The left submandibular gland had a clearance of -6.6% (Fig 3).

A classic right submandibular incision was made 4.0 cm below the border of the mandible, making a skin platysma flap. The vital vasculature (facial artery and vein, in addition to lingual artery) were double ligated and severed. An extracapsular excision of the gland was performed. The spec-

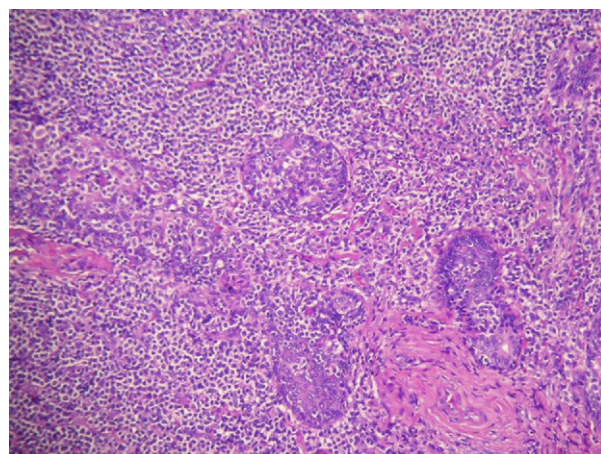


FIGURE 5. Histologic appearance of the right submandibular gland showing lymphoepithelial tissue (hematoxylin-eosin stain, 20 \times).

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imen was submitted for histological evaluation (Fig 4). One Jackson Pratt drain was placed and removed 1 day after the surgery because of a lack of drainage. The patient experienced an uneventful postoperative recovery.

The biopsy results were consistent with extranodal marginal zone B cell lymphoma (mucosa-associated lymphoid tissue lymphoma). The hematoxylin and eosin section of the specimen showed a large lympho-epithelial lesion surrounded by normal appearing salivary glands. The nodules were composed of small- to medium-sized lymphoid cells with monocytic features (Figs 5 and 6). The immunohistochemistry results were positive for CD20 (Fig 7) and CD43 and negative for CD10, CD5, CD23, and BCL-1. Some sections tested positive for scattered cells highlighted by CD3 staining. In addition, a few CD23 positive follicular dendritic cells were present in the study.

The patient was referred to the Hematology Oncology Department for further workup and treatment. Although the

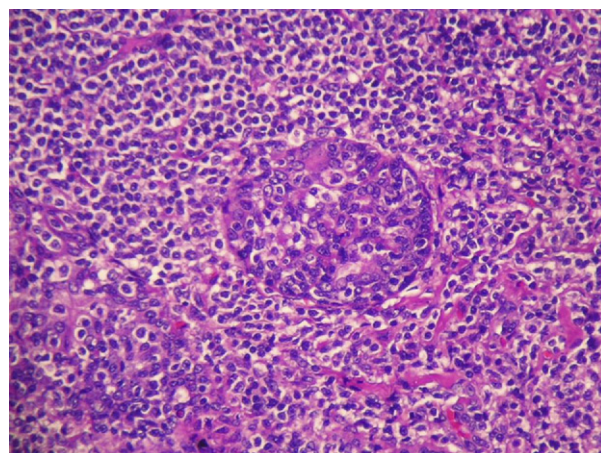


FIGURE 6. Histologic characteristics of the right submandibular gland, focused in 1 epithelial island (hematoxylin-eosin stain 40 \times).

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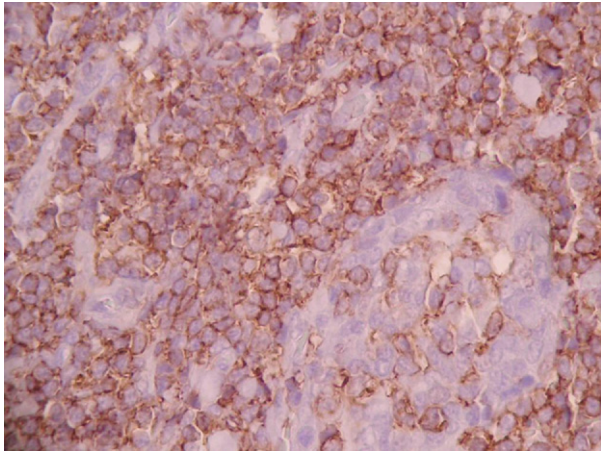


FIGURE 7. Immunohistochemistry positive for CD 20 marker in B-cells (40 \times).

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patient's eyes were clinically asymptomatic, recommendation was made to follow with an ophthalmologist for further studies such as the Schirmer's test and Rose-Bengal score. A rheumatology consult was requested for autoantibody series tests to rule out other autoimmune diseases.

Patient failed to follow up with ophthalmology and rheumatology services. The Hematology and Oncology Department performed multiple standard diagnostic workups for establishment of oncological staging and treatment modality.

Test results were negative for *Helicobacter pylori* bacteremia, intestinal metaplasia, and any lymphoma-related changes of gastrointestinal tract. A bone marrow biopsy revealed no evidence of lymphoma. A CT scan of chest, abdomen, and pelvis was negative. However, a positron emission tomography scan was positive for enlarged jugulo-digastric, internal jugular, and spinal accessory chain lymph nodes. The Waldeyer's ring, which is a common site for MALT type lymphoma, showed increased glucose metabolism. Additionally, hypercaptation was noted in the endometrium and pelvis (Fig 8).

According to the National Comprehensive Cancer Network and the Ann Arbor staging system, this case was considered a

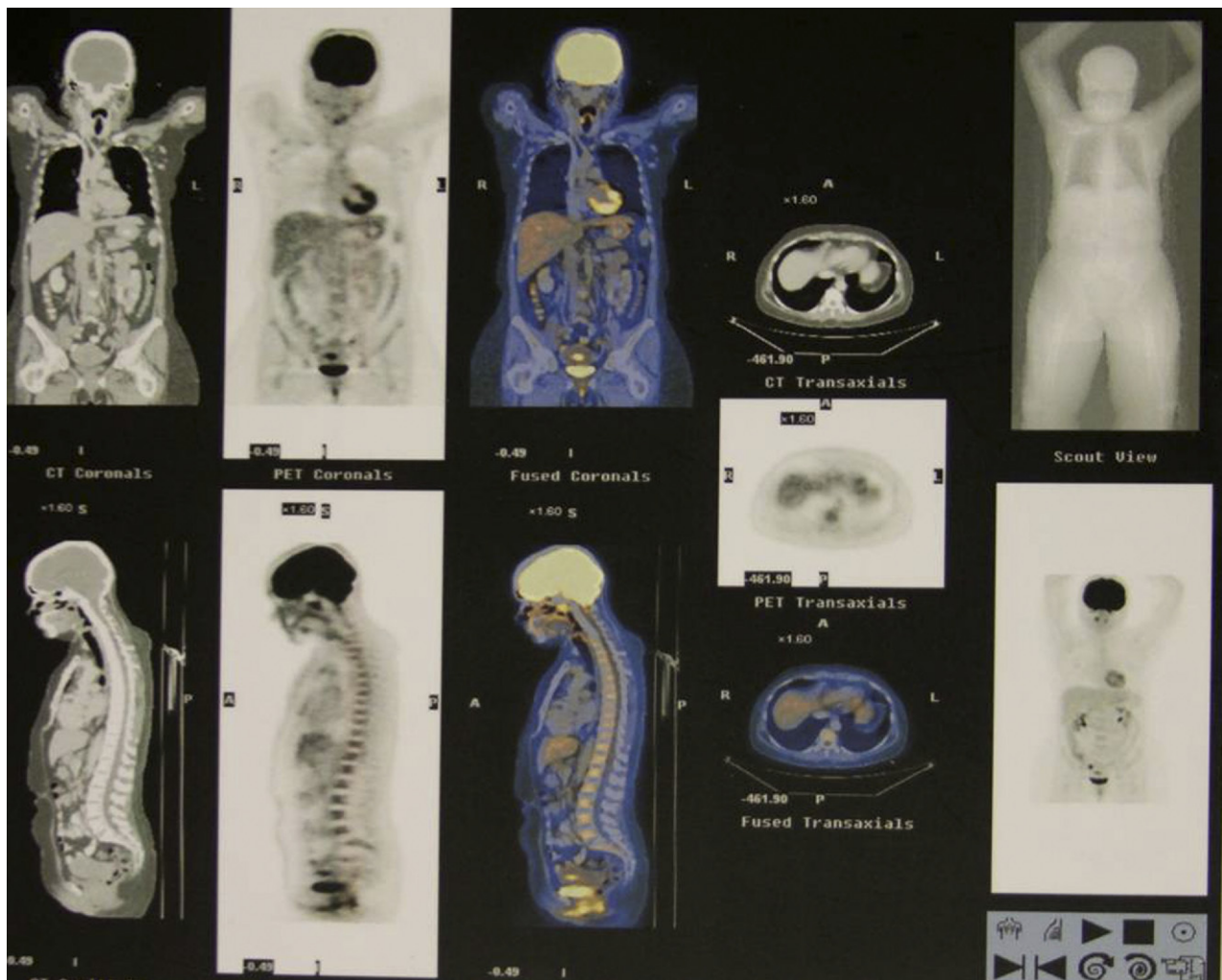


FIGURE 8. Whole-body positron emission tomographic scan revealing hypermetabolism.

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stage III MALT type lymphoma because of the existence of extranodal sites, multiple nodal sites, and the presence of disease above and below the diaphragm. As per guidelines used in our institution, given the toxicity of radiotherapy and chemotherapy, the decision was made to observe the patient with no intervention. Any further treatments and diagnostic studies were recommended on the basis of future end organ dysfunction. As of the patient's last visit (1-year status postdiagnosis of lymphoma), the patient was asymptomatic with no lymphadenopathy or palpable masses of the neck region.

Discussion

MALT lymphoma of the salivary glands is not common. In the major glands, it is more often located in the parotid compared with the submandibular gland. Certain histological features of MALT lymphoma—including the presence of B cells, tumor lymphocytes, and the presence of scattered transformed blasts—suggest involvement of the immune response. The immune response could be elicited by a chronic infectious process or could be autoimmune in nature. In primary SS, predisposition of the patient for development of non-Hodgkin's lymphoma (4% to 10%), which occurs later in the course of the disease, is well established.⁴ Whether secondary SS also predisposes the patient to lymphoma remains unclear. In our presented case, long-standing sialadenitis could be the aggravating etiological pathology in addition to the later diagnosed SS. With a 5-year survival rate of 97% associated with treatment modalities, Ann Arbor stages I and II of MALT-type lymphomas of major salivary glands have a favorable prognosis. The nongastric MALT-type lymphomas with established Ann Arbor stages of III and IV have a 5-year survival rate of 93.8%, and the progression-free survival is 70.1%.¹³ In cases of chronic infection of salivary glands and the presence of autoimmune syndromes, MALT lymphoma should be considered in the differential diagnosis. When indicated properly, directed consults should be called to ophthalmology and rheumatology to assess ocular involvement and presence of other autoimmune diseases. MALT lymphoma can

only be confirmed by biopsy. At the time of diagnosis, the patient should be referred to a head and neck oncologist for proper workup, staging, and treatment. Additionally, the oral and maxillofacial surgeon should continue to follow the patient throughout their treatment. The 5-year follow-up period after diagnosis of the disease is of importance, and the patient should be screened for possible treatment failures and the development of new disease.

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