

## Non-Hodgkin's Lymphoma & Primary Biliary Cirrhosis with Sjögren's Syndrome

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Sjögren's syndrome (SS) is an autoimmune disease characterized by a lymphocytic infiltration of the salivary and lacrimal glands leading to a progressive destruction of these glands due to the production of autoantibodies. This disorder is either isolated (primary SS) or associated with other systemic diseases (secondary SS). The occurrence of B-cell non-Hodgkin's lymphoma (NHL) represents the major complication in the evolution of SS patients. The risk of developing NHL, which is equivalent for both primary and secondary SS, was estimated to be 44 times greater than that observed in a comparable normal population. NHLs in SS patients occur preferentially in the salivary glands and in other mucosa-associated lymphoid tissues (MALT). However, it can also occur in the lymph nodes or bone marrow.

We documented a case of low-grade B-cell lymphoma of MALT in the right eyelid and primary biliary cirrhosis (PBC) of a patient with SS. To the best of our knowledge, this is the first case reported in Korea.

**Key Words:** Sjögren's syndrome, non-Hodgkin's lymphoma, PBC, eyelid

### INTRODUCTION

Sjögren's syndrome (SS) is a chronic autoimmune disease associated with the production of autoantibodies and is characterized by a progressive lymphocytic and plasma cell infiltration of the salivary and lacrimal glands leading to xerostomia and xerophthalmia. SS may be primary or associated with another autoimmune disease, most frequently with rheumatoid arthritis (secondary SS). The spectrum of primary SS extends broadly from an organ-specific autoimmune disorder (autoimmune exocrinopathy) to a

systemic process involving the musculoskeletal, pulmonary, gastrointestinal, hematological, vascular, dermatologic, renal, and nervous systems.<sup>1</sup> A well-known association exists between autoimmune diseases and lymphoid malignancies. Malignancy, mainly B-cell NHL (B-NHL), may develop in autoimmune diseases.<sup>2,3</sup>

Although the lifetime incidence of overt NHL in autoimmune diseases is normally below 10%, the relative risk (RR) is high, as reported in Hashimoto thyroiditis (RR is 70), systemic lupus erythematosus (RR is 44), SS (RR is 44), and rheumatoid arthritis (RR is 24).<sup>4</sup> Autoantibodies may be detected in the serum of patients with B-cell proliferations including non-Hodgkin's lymphoma (NHL) and multiple myeloma.

We documented a case of low-grade B-cell lymphoma of MALT in the right eyelid with SS. To the best of our knowledge, this is the first case reported in Korea.

### CASE REPORT

A 61-year-old female was admitted to our hospital with xerostomia, xerophthalmia, myalgia and arthralgia. Her family history is unremarkable with no known genetic diseases.

The physical examination on admission revealed the following: blood pressure 120/80 mmHg; pulse rate 82/min; respiration rate 20/min; and body temperature 36.4°C; Movable, non-tender, 0.3 cm-sized, multiple lymph nodes were palpated on the right neck. There was no hepatosplenomegaly.

Laboratory tests revealed the following: hemo-

globin, 10.2 g/dl; hematocrit, 29.6%; white cell count (WBC), 3,800/ul with 54.5% polymorphonuclear cell; platelet count, 152,000/ul; calcium, 8.3mg/dl; phosphate, 3.6 mg/dl; blood urea nitrogen, 8.8 mg/dl; creatinine, 0.7 mg/dl; total protein, 6.5 g/dl; albumin, 2.5 g/dl (3.3 – 5.3); globulin level, 4.0 g/dl; total bilirubin, 3.4 mg/dl (0.2 – 1.2); direct bilirubin, 2.2 mg/dl; alkaline phosphatase, 518 IU/L (38 – 115); AST, 327 IU/L (13 – 34); ALT, 22 IU/L; the r-GT, 207 IU/L (12 – 54); uric acid, 2.8 mg/dl; LDH, 321 IU/L (225 – 425) with a normal pattern of LDH isoenzymes; erythrocyte sedimentation rate (ESR), 40 mm/hr (<15); rheumatoid factor (RF), 72.0 IU/ml' (<20);  $\beta_2$ -microglobulin, 6.5 mg/L (0.8 – 2.0); gamma globulin, 2.71 g/dl (polyclonal gammopathy); anti-mitochondrial antibody, positive. Additional laboratory tests revealed the following: Anti-DNA and anti-nuclear antibody, negative; the Anti-Ro/Anti-La, negative; HBs-Ag, negative; anti-HCV, negative. The findings of the Shirmer's test was positive in both eyes.

An X-ray of the chest showed bilateral overinflation and diffuse bronchial wall thickening. An orbital CT scan showed an enlargement of the lacrimal gland in the superiolateral aspect of the right orbit (Fig. 1A). This lesion was relatively homogenous in density with dirty infiltration involving the eyelids. The abdomino-pelvic CT scan showed mild fluid collection in the pelvic cavity with no significant lymphadenopathy or with slightly enlarged lymph nodes at the left paraaortic area, although the liver was found normal.

The microscopic findings of the biopsied minor

salivary gland in the lower lip showed a dense parenchymal lymphocytic infiltration, consistent with SS (Fig. 2). The biopsy tissue in the right superior eyelid showed a sheet-like proliferation of centrocyte-like cells, which are small lymphoid cells with slightly irregular nuclei and relatively abundant pale cytoplasm, typical of the low-grade B-cell lymphoma of MALT (Fig. 3). Peritoneoscopic biopsied liver tissue showed cirrhosis with severe lobular necroinflammatory activity and areas of lobular collapse (Fig. 4), prominent ductular proliferation, and injury of the bile duct epithelium (Fig. 5).

After being diagnosed as, SS in September of 1997, corticosteroid was given for the treatment of swelling of the parotid gland and eyelid. Starting on day 1, 15 mg/day prednisolone (PL) was administered until day 67 when 15 mg and 12.5 mg were then given on alternate days. On day 125, PL dose was reduced to 12.5 mg and 10 mg given on alternate days. On day 152, 12.5 mg and 7.5 mg were given on alternate days. She, then complained of phalangeal and knee joint pain and a daily dose of 400 mg of hydroxychloroquine was also administered. Beginning on April 13, 1998, PL was reduced to 12.5 mg and 5 mg given on alternate days. To ameliorate xerophthalmia, topical ophthalmic solution was applied 3 to 4 times daily on the eyes.

Radiation therapy was performed for right eyelid malignant lymphoma (stage IE) upon diagnosis. After being diagnosed as a low grade B-cell lymphoma of MALT in December of 1998, a total of 3,060 cGy was irradiated and a follow-up orbital CT scan on the irradiated eye confirmed

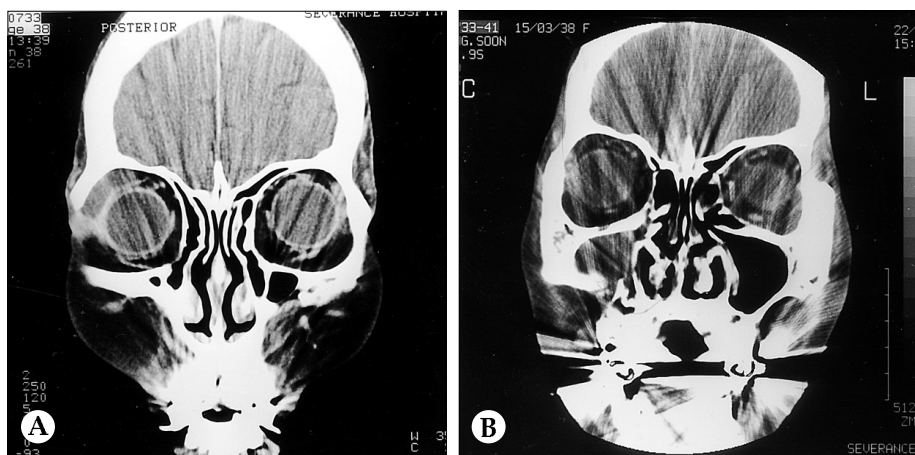
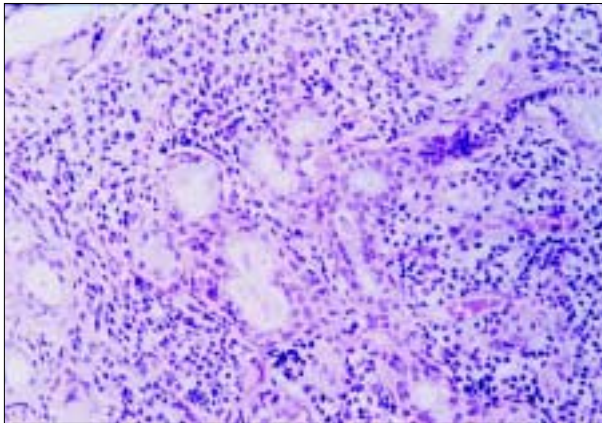
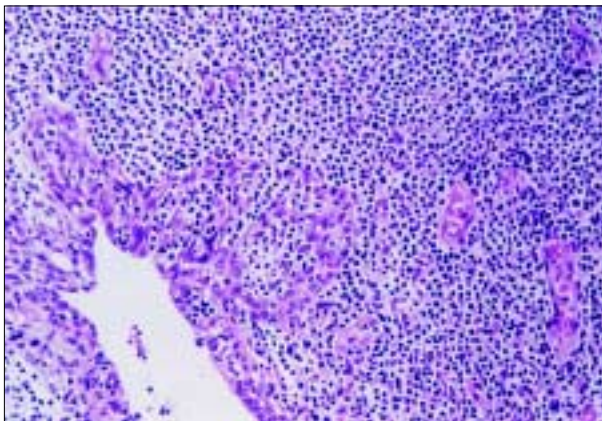


Fig. 1. A. The initial orbital CT scan showed enlargement of the lacrimal gland in the superiolateral aspect of the right orbit. B. The follow-up orbital CT scan showed no evidence of tumor recurrence in the right orbital area.



**Fig. 2.** The microscopic finding of the minor salivary gland in the lower lip shows a dense parenchymal lymphocytic infiltration, consistent with Sjögren's syndrome (H&E × 200).

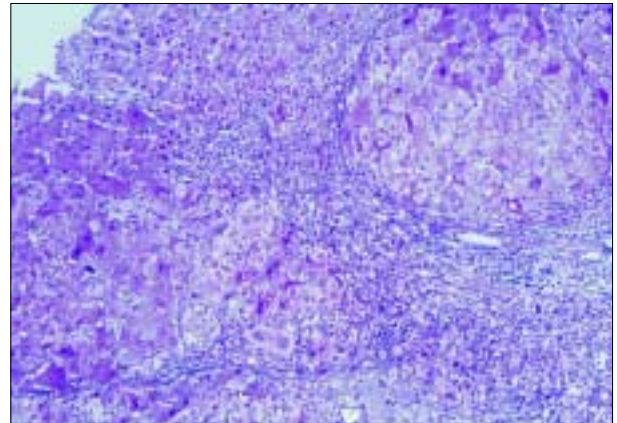


**Fig. 3.** The microscopic finding of the mass in the right upper eyelid area shows a sheet-like proliferation of centrocyte-like cells typical of the low-grade B-cell lymphoma of MALT (H&E, ×200).

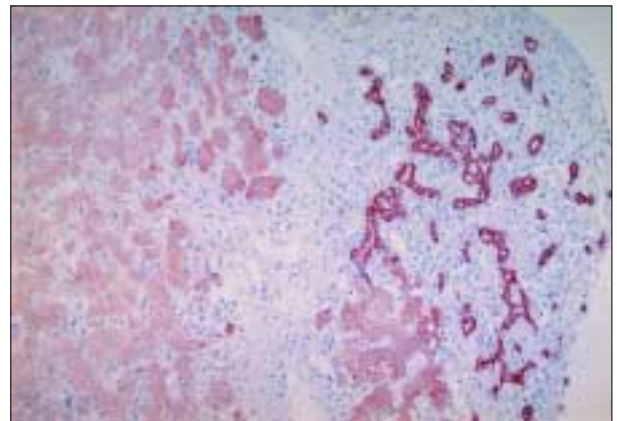
the complete remission of the malignant lymphoma (Fig. 1B). The patient has been receiving treatment for liver cirrhosis but there is no evidence of recurrent lymphoma 8 months after the cessation of radiation treatment.

## DISCUSSION

The appearance of clinical symptoms of SS is very complex and it is thus often difficult to accurately diagnose. Different diagnostic standards have been used according to individual preferences.<sup>5,6</sup> The First International Conference of SS was held in 1986, at Copenhagen, Denmark,



**Fig. 4.** Microscopic finding of the peritoneoscopic biopsied liver tissue showing liver cirrhosis with severe lobular necroinflammatory activity and areas of lobular collapse (Trichrome, ×100).



**Fig. 5.** Immunohistochemical staining for low molecular weight cytokeratin (AE1) showing prominent ductular proliferation and damage of the bile duct epithelium (LSAB, AEC with hematoxylin counterstain, ×100).

and new diagnostic and classification standards of SS were proposed.<sup>7</sup> The diagnosis of "definitive SS" would be made when the following criteria are met after excluding preexisting lymphoma, graft-versus-host disease, sarcoidosis and acquired immunodeficiency syndrome. The four absolute criteria are 1) objective evidence of keratoconjunctivitis sicca, as documented by rose bengal or fluorescein dye staining; 2) objective evidence of diminished salivary gland flow; 3) minor salivary gland biopsy, obtained through normal mucosa, with the specimen containing at least 4 evaluable salivary gland lobules, and having an average of at least 2 foci/4 mm<sup>2</sup>; and 4) evidence of a systemic autoimmune process, as manifested by the

presence of autoantibodies, such as rheumatoid factor and/or antinuclear antibody. "Possible SS" would be diagnosed if three out of four of the absolute criteria were met with exclusion of the 4-four aforementioned conditions. This case has fulfilled the diagnostic criteria for definitive SS. SS typically develops in the elderly around the fifth decade and occurs more often in women with a ratio of up to 10 : 1.<sup>8</sup>

The systemic manifestations in primary SS are protean and musculoskeletal manifestations include arthralgia, arthritis, and myositis. Skin manifestations include photosensitivity, purpura, urticaria-like disease, vasculitis, alopecia, and erythema nodosum. Pulmonary involvement manifests as interstitial and obstructive disease and pleuritis. Dysphagia, atrophic gastritis, primary biliary cirrhosis, nonviral autoimmune chronic hepatitis, and nonalcoholic pancreatitis are gastrointestinal manifestations and renal manifestations presents as involvement tubular acidosis, interstitial nephritis, and glomerulonephritis. Other systemic manifestations in primary SS are neurologic manifestations, Raynaud's disease, malignant lymphoma.<sup>9</sup>

The systemic manifestation found in this case were; musculoskeletal symptoms, obstructive lung disease, liver cirrhosis and malignant lymphoma. According to the reports by Kelly et al.,<sup>10</sup> 24 out of a total of 100 cases of SS patients showed GI symptoms, 3 cases demonstrated primary biliary cirrhosis and 3 cases displayed malignant lymphomas. The peritoneoscopic biopsy findings of this case, such as severe lobular necroinflammatory activity and areas of lobular collapse is compatible with hepatitis, concomitant with liver cirrhosis. A viral marker test was negative and the patient had no history of alcoholic or specific drug ingestion. Histologic evidence of bile duct injury and prominent ductular proliferation highlighted by immunohistochemical stain for AE1 in conjunction with the positive anti-mitochondrial antibody test is compatible with primary biliary cirrhosis. Therefore, this case strongly favored the overlapping features of autoimmune hepatitis and primary biliary cirrhosis (stage IV) accompanying SS.<sup>11</sup>

Hematologically, SS presents with anemia in 25% of cases and leukopenia in 30% of cases and

notably, more than 90% of the patients have increased ESR.

Immunogenotypic analysis techniques such as Southern blot analysis, polymerase chain reaction, and in situ hybridization have been used to analyze the nature of lymphoid cell infiltration from SS patients. They show oligoclonal or monoclonal B cell expansion in 14% to 100% of cases.<sup>9,12-14</sup> Some of these patients have developed overt NHL. This indicates that SS is a crossroad between autoimmunity and malignancy, and that monoclonality may be a precursor for NHL development. Monoclonality of lymphoid cells in SS arises mainly from the salivary glands, but may arise also from visceral organs and lymph nodes.

Factors associated with monoclonal or malignant transformation during the course of disease are not fully understood. However, dysregulation in the mechanisms leading to apoptosis, hyperstimulation of B-1 cells, or an infectious agent may contribute to malignant lymphoproliferation in SS.<sup>15,16</sup>

The clinical and biological findings suggesting NHL arising in SS include persistent enlargement of parotid glands, splenomegaly, persistent lymphadenopathy, mediastinal or hilar lymph nodes, lung nodules, recurrent fever, monoclonal gammopathy, mixed cryoglobulinemia (type II), cross-reactive idiotypes, lowered serum IgM, high serum  $\beta_2$ -microglobulin, and negative conversion of rheumatoid factor.<sup>14</sup>

If malignancy is clinically suggested in an SS patient, a biopsy must be performed to rule out NHL, particularly in patients whose main complaint is persistent parotid gland swelling, a parotid biopsy should be considered instead of minor salivary biopsy.<sup>17</sup>

In September of 1997, in the course of corticosteroid treatment, a tumor on the right eyelid was palpated. In addition persistent enlargement of the parotid glands and high serum  $\beta_2$ -microglobulin were found to suspect a development of lymphoma. A tissue biopsy in the right superior eyelid has shown the typical histologic findings of a low-grade B-cell lymphoma of MALT.

Various kinds of malignant tumors, such as lung cancer, breast cancer,<sup>10</sup> can accompany SS. However, the most common SS associated tumors

are of low-grade B cell lymphomas such as mantle cell lymphoma (MCL), follicle center lymphoma (FCL), small lymphocytic lymphoma (SLL), lymphoplasmacytoid lymphoma/immunocytoma, and marginal zone B-cell lymphoma (MZL) including low-grade B cell lymphoma of mucosa-associated lymphoid tissue (MALTOMA)/ monocytoid B cell lymphoma (MBCL).<sup>12,18,19</sup>

It has been reported that the probability of developing malignant lymphoma in primary SS is about 5 – 8%.<sup>9</sup> On the other hand, in a series of 113 cases with NHL, 14 (12%) met the criteria for primary SS.<sup>20</sup> Additionally, NHL has been implicated in the development of SS-like illness.

The treatment for SS is primarily by conservative care. Focal damage due to chronic dryness of the eyelids and xerostomia which are of cardinal concern is treated with sialogogue or artificial saliva and teardrop solutions. For the cases of severe disability where life threatening complication may occur, adrenocorticosteroids or immunosuppressive therapy may be used. In this case, symptomatic treatment along with adrenocorticosteroids for swelling in the parotid gland and in the eyelids was done.

The treatment and prognosis of SS-associated NHL depend on the type and stage of lymphoma.<sup>21,22</sup> Patients with low-grade lymphomas affecting exocrine glands should be completely evaluated for the extent of the disease. Surgical resection is essential for accurate histological assessment and staging extranodal NHL, but also may be curative in histologically low-grade and lower stages (I/II) NHL.<sup>23</sup> If the tumor cannot be totally resected, radiation therapy should be considered. However, in NHL of the parotids gland, there is no consensus on the use of radiotherapy, because painful oral mucositis and exacerbation of preexisting xerostomia may result.<sup>17</sup> The 5 year survival rate in low-grade B-NHL associated with SS generally is greater than 50%.<sup>9</sup> In high-grade and clinically aggressive malignancy, combination chemotherapy and radiation therapy are recommended. CHOP protocol (cyclophosphamide, doxorubicin, vincristine, prednisone) is the treatment of choice for patients with advanced intermediate-grade or high-grade NHL.<sup>24</sup>

Hahn et al.<sup>25</sup> reported that radiotherapy alone

has demonstrated 90% remission on primary eye lymphoma. This case received radiotherapy and is now under close observation without recurrence for 8 months.

The development of non-Hodgkin's lymphoma is a well-known complication of SS. Most of these are low grade B-cell lymphoma of mucosa-associated lymphoid tissue or diffuse large B-cell lymphoma arising from the salivary glands. We have described a case of low-grade B-cell lymphoma of MALT in the right eyelid in a patient with SS, which is very rare and has never before been reported in Korea.

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