A Case of Non-Hodgkin’s Lymphoma of the Ocular Adnexa and Lung in a 17-year-old with Primary Sjögren’s Syndrome

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Sjögren’s syndrome (SS) is a chronic autoimmune disorder characterized by lymphocyte-mediated destruction of exocrine glands, which produces classical symptoms of dry eyes and dry mouth. Aside from the clinical manifestations associated with exocrine glands, extraglandular features of SS include a major long-term concern for development of lymphoma. The lifetime risk of non-Hodgkin’s lymphoma (NHL) in an SS patient is approximately 5% to 10%, 20 times higher than that of the normal population. This case report describes a rare occurrence of NHL in the eyelid and lung of an adolescent female with SS, whose disease activity had been monitored closely. This is the first reported case in Korea. (J Rheum Dis 2016;23:61-65)

Key Words. Sjögren’s syndrome, Lymphoma, Conjunctiva, Lung

INTRODUCTION

Sjögren’s syndrome (SS) is a systemic autoimmune disease that mainly affects the exocrine glands and usually presents as persistent dryness of the mouth and eyes due to functional impairment of the salivary and lachrymal glands. In addition, a variety of other disease manifestations can occur in SS and are divided into exocrine gland features and extraglandular features. Among the extraglandular features, a major long-term concern for patients is the development of lymphoma. Malignant lymphoma was first reported in patients with SS in 1963. A case report supports the association of lymphoma with SS and recognizes malignant non-Hodgkin’s lymphoma (NHL) as a major complication in the progression of the disease [1]. The estimated lifetime risk of NHL in an SS patient is approximately 5% to 10%, which is 20 times higher than that of the normal population [2]. Lymphomas complicating SS are mostly low-grade B cell NHLs, particularly extranodal marginal zone of mucosa-associated lymphoid tissue (MALT) lymphomas. Salivary glands are the most frequent location of MALT lymphomas in SS, but other mucosal sites can be affected, such as orbits, nasopharynx, stomach, thyroid, and lung [3]. In Korea, there has been only one reported case of conjunctival involvement [4]. This case report describes a rare occurrence of NHL in the ocular adnexa and lung of a 17-year-old primary Sjögren’s syndrome (pSS) patient.

CASE REPORT

A 17-year-old female patient had been followed in the Department of Rheumatology for SS since 2012. She had suffered from recurrent parotitis every 5 to 6 months since 2009. She complained of dry mouth and dryness in the oral cavity and experienced aggravation of dental caries. She visited the Department of Otolaryngology in 2012 for parotid gland swelling and was admitted for evaluation. Laboratory examination revealed white blood cell count 2,700 cells/mm³, neutrophil count 1,463 cells/mm³, hemoglobin 10.0 g/dL, and platelet 182,000 cells/mm³. Erythrocyte sedimentation rate was 60 mm/h.
and C-reactive protein was 0.388 mg/dL. Serum C3 level was 117 mg/dL (90 to 180 mg/dL) and C4 level was 17.4 mg/dL (10 to 40 mg/dL). Based on her previous history, a further work up for SS was performed, including an anti-nuclear antibody (ANA) profile and rheumatoid factor (RF) assessment. ANA showed a speckled pattern with a ratio of 1:320. RF was increased to 317 IU/mL. SSA and SSB were positive. As she was an adolescent who had not been taking any medicines, drug induced or age related xerostomia seemed less likely. Infectious parotitis was also less likely because she did not have any constitutional symptoms such as high fever, pain or tenderness of swollen parotid gland. Schirmer’s test with a wetness score <5 mm for the eyes, xerostomia with recurrent parotitis and positive autoantibodies were suggestive of pSS, according to the American-European Consensus Sjögren’s classification criteria [5]. She did not exhibit any signs and symptoms such as alopecia, arthritis, oral ulcers, skin rash or Raynaud’s phenomenon that suggest other primary rheumatic disorders. She was finally diagnosed with pSS after labial salivary gland biopsy exhibited focal lymphocytic sialadenitis. She was prescribed hydroxychloroquine and methylprednisolone in the Department of Rheumatology, and her symptoms improved.

In April 2014, she visited the clinic with a chief complaint of a small nodular mass on the conjunctiva of the lower eyelid. She complained of a foreign body sensation due to the mass and worsening xerophthalmia. On general physical examination, she did not have any enlarged lymph nodes and was without constitutional symptoms. She was referred to the Department of Ophthalmology for further evaluation. Both eyes had full vision and normal intraocular pressure and there was no decreased visual acuity, ptosis, or diplopia. A solitary mass, which measured approximately 0.5×0.5 cm, was noticed on the conjunctiva of the right lower eyelid. The mass was non-tender and fixed. Considering the possibility of malignancy, the patient underwent an orbital computed tomography (CT) scan (Figure 1). CT showed no abnormal findings in the orbits, eyeballs, extraocular muscles, or optic nerves. Complete mass resection was performed by an ophthalmologist. This mass clinically resembled a pyogenic granuloma. However, considering she was a pSS patient, surgical biopsy and immunohistochemistry were performed to exclude lymphoma. Sections from the lesions, which were stained with hematoxylin and eosin, revealed atypical lymphoid cells with mitosis and a loss of normal lymphoid architecture (Figure 2). Immunohistochemistry was performed for the exact typing of the lymphoid lesion (Figure 3). The lymphoid cells were positive for CD20, CD79a, and Bcl-2 but negative for CD3, Cyclin D1, and CD56. We confirmed the diagnosis of extranodal marginal zone B cell lymphoma of mucosa associated lymphoid tissue (MALT lymphoma). After being diagnosed with malignant NHL, the patient was admitted to the Department of Hematology to evaluate for any disseminated disease. She underwent laboratory studies, chest, abdomen CT scans, bone marrow biopsy, and a positron emission tomography (PET) scan. Laboratory data were as follows: white blood cell count 4,790/μL, neutrophil count 1,834 cells/mm³, hemoglobin 10.5 g/dL, platelet count 155,000/cm², serum albumin 4.7 g/dL, uric acid 5.6 mg/dL, creatinine 0.87 mg/dL, lactate dehydrogenase (LDH) 317 IU/L (263 to 450 IU/L), and β2 microglobulin 2.44 mg/L (1.0 to 2.4 mg/L). Plain radiography of the chest showed no appreciable abnormalities. However, chest CT demonstrated multifocal patchy consolidations and ground glass opacities in

![Figure 1. Orbital computed tomography scan (A, B) showed no abnormal findings in the orbits, eyeballs, extraocular muscles, or optic nerves.](image-url)
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Figure 2. Conjunctival lymphoid tissue. H&E stained sections showing abnormal lymphoid architecture and atypical lymphoid cells with mitosis (A: ×40, B: ×400).

Figure 3. Immunohistochemistry showing extensive, dense, packed CD20 B-cell lymphoid infiltrate (immunohistochemistry with hematoxylin counterstain, ×400).

Figure 4. Multifocal patchy consolidations and ground glass opacities in the right middle lobe (arrow).

the right middle lobe of the lung (Figure 4). Abdomen CT and bone marrow biopsy results were normal. PET scan showed no definite focal abnormal hypermetabolic lesions suggesting a malignant process. Video-assisted thoracic surgery was performed on the consolidative lesion in the right middle lobe of the lung. The biopsy specimen revealed MALT lymphoma. According to the National Comprehensive Cancer Network (NCCN) guidelines for NHLs, she was diagnosed with stage IV lymphoma [6].

In June 2014, she started combination systemic chemotherapy with rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP). In December 2014, she completed the scheduled 8 cycles of chemotherapy without noticeable side effects and underwent a chest CT, PET scan, and ophthalmologic examination to evaluate the response to therapy. Both the chest CT scan and PET scan showed no evidence of remnant lymphoma involvement in her lungs. The conjunctival biopsy site was also clear without local tumor relapse. We confirmed complete remission, and she is now being followed regularly in the Departments of Hematology and Rheumatology without further chemotherapy.

DISCUSSION

The incidence of lymphomas in various studies of patients with SS has ranged from 4.3% to 10% [1,7]. Patients with SS have up to a 20-fold increased risk of developing lymphoma relative to the general population.
Lymphomagenesis in pSS patients is considered as a multistep process. Chronic stimulation by exoantigen or autoantigen plays an important role in the development of lymphoma by driving the proliferation of specific B cells and increasing the frequency of their transformation [8]. Recent studies have focused on the role in pSS pathogenesis of B-cell activating factor (BAFF), a member of the tumor necrosis factor superfamily, also called the B lymphocyte stimulator, and the proliferation inducing ligand (APRIL), which participates in B-cell activation [8]. The BAFF/APRIL system regulates B-cell survival, differentiation and proliferation. Both BAFF and APRIL are over expressed in pSS patients. The over expression of BAFF in infiltrated salivary glands may contribute to B cell survival, aggregation, altered differentiation and tolerance, as well as in lymphoma development [8]. Cytokine stimulation, environmental factors, viral infection are possible factors that may contribute to the development of lymphoma. 

Lymphomas complicating SS are mostly low-grade B cell NHLs, particularly MALT lymphomas [2]. MALT lymphomas are extranodal B-cell tumors that account for 8% of all NHLs [9]. The gastrointestinal tract is involved in around 50% of cases and the stomach is the most common location [9]. They arise also from various non-gastrointestinal sites, such as salivary gland, conjunctiva, thyroid, orbit, lung, breast, kidney, skin, liver, and prostate. Thieblemont et al. [10] reported 18 cases (11.3%) out of 158 patients of MALT lymphoma that had multiple MALT organ localization. Only 1 patient (0.75%) presented with lung and orbit involvement at diagnosis as our patient did [10].

In a patient with SS, ocular adnexa is a very rare lesion for lymphoma development. Salivary glands are the most common site of lymphoma development, but extranodal sites are also involved, including the stomach, nasopharynx, liver, lungs, lymph nodes and bone marrow [8]. To the best of our knowledge, there has been only one similar case report in Korea. Hahn et al. [4] reported a case of low-grade B-cell MALT lymphoma on the right eyelid and primary biliary cirrhosis of a patient with SS. Differences between our case and the previously reported one are that our patient was an adolescent, and she also presented with lung involvement.

Certain clinical and immunological characteristics of SS patients have been described as lymphoma predictors [2,3]. The main clinical predictors are recurrent swelling of salivary glands, lymphadenopathy, and skin involvement, especially palpable purpura. The main biological predictors are cryoglobulinemia, neutropenia, low complement levels, and a monoclonal component in serum or urine. It is recommended for active disease or in the presence of several risk factors, that SS patients be closely monitored for lymphoma with screening every 6 months [3]. This 17-year-old pSS patient presented with swelling of the parotid gland and neutropenia (1,463 neutrophil cells/mm³) at diagnosis. During her regular clinic visits before the diagnosis of lymphoma, she consistently had low neutrophils, most of the times less than 2,000 cells/mm³. Neutropenia did not worsen markedly over time and serum C3 and C4 levels were always within normal range. Although her conjunctival mass resembled a pyogenic granuloma, we performed a thorough investigation because she was an SS patient who had risk factors for developing lymphoma.

Most cases of NHLs that arise in the ocular adnexa are MALT lymphomas [11]. McKelvie et al. [11] reported that the major histological types were MALT (63%), follicular (17%), diffuse large B-cell (11%), and mantle cell (3%) lymphomas. The global outcome of MALT lymphoma of ocular adnexa is generally favorable. Advanced stage disease, age greater than 64 years, presence of B symptoms, nodal involvement, non conjunctival sites, and an elevated serum LDH level have been identified as poor prognostic factors [12].

MALT lymphomas of the lung are very rare malignancies. Papiris et al. [13] reported clinical, radiological, and pathology findings of MALT of the lung in SS patients. The radiographic features of MALT in SS patients were non-specific, and the most common findings on chest X-rays were patchy infiltrates [13]. The disease was detected on routine or occasional examination in all cases, and a mild, dry cough was the chief complaint leading to chest imaging [13]. Routine chest X-ray should be regularly performed in SS patients; if pulmonary infiltrates are noted, further investigation for lung lymphoma is necessary. The optimal treatment in the absence of any prospective studies remains unclear. In localized MALT lymphomas of the lung, surgical resection, either alone or in combination with chemotherapy, has been the mainstay of treatment [14]. The overall response to treatment is satisfactory and prognosis is favorable.

In patients with limited stage ophthalmologic lymphoma and no risk for visual impairment, radiotherapy is considered the treatment of choice [12]. As the patient in this case presented with lung involvement, she was diagnosed...
with advanced stage lymphoma. Advanced stage extranodal marginal zone B-cell lymphoma is treated primarily with systemic chemotherapy, such as cyclophosphamide, vincristine and prednisolone (CVP) plus the recombinant anti-CD20 antibody (rituximab). Combination chemotherapy with R-CVP achieves a high response rate and less toxicity with early disease control in patients with newly diagnosed advanced stage marginal zone B-cell lymphoma [15].

In this case, advanced stage lymphoma would not have been diagnosed if a thorough systemic investigation had not been performed for the patient’s small conjunctival mass. This shows that, even when an SS patient presents with a small mass in a location where lymphoma is unlikely to develop, investigation for lymphoma is crucial. Regular patient assessment using lymphoma predictors can be beneficial for lymphoma screening.

**SUMMARY**

We reported a rare case of a 17-year-old patient with pSS with conjunctiva and lung lymphoma. This case suggests that, in a SS patient with an ocular adnexal mass, a surgical biopsy with immunohistochemistry must be considered in order to exclude lymphoma. After lymphoma is diagnosed, additional investigation is needed to evaluate for systemic involvement.

**CONFLICT OF INTEREST**

No potential conflict of interest relevant to this article was reported.

**REFERENCES**