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□ Case Report □

Remission of Lymphocytic Interstitial Pneumonia in Sjögren's Syndrome after Autologous Peripheral Blood Stem Cell Transplantation

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Interstitial pneumonia occurs in approximately 25% of patients with primary Sjögren's syndrome. Interstitial pneumonia combined with primary Sjögren's syndrome usually responds well to systemic steroids, and fatal cases are rare. Lymphocytic interstitial pneumonia shows diffuse infiltration of polyclonal B and T cells. Autologous stem cell transplantation is performed in cases of primary Sjögren's syndrome as an optional treatment when the condition responds poorly to conventional treatment. The hypothesis that primary Sjögren's syndrome improves after transplantation relies on the role of B-cell abnormalities in pathogenesis or the strong effects of immunosuppressive therapy. We experienced the case of a patient diagnosed with primary Sjögren's syndrome and lymphocytic interstitial pneumonia progression refractory to conventional treatment (steroid and immunosuppressive drugs) and cyclophosphamide pulse therapy. Our patient demonstrated improvement of lung manifestations and autoimmune disease activity after autologous stem cell transplantation.
Key Words. **Sjögren's syndrome, Lymphocytic interstitial pneumonia, Stem cell transplantation**

Introduction

Primary Sjögren's syndrome (pSS) is a systemic inflammatory disease that involves the exocrine glands, including the salivary and lacrimal glands. Although the most important clinical symptom of this disease is dryness of the mouth, pSS can cause systemic extraglandular symptoms. Involvement of the lungs, although it is found in more than 50% of patients, is usually asymptomatic. However, lung involvement appears as the initial accompanying symptom in about 10% of patients (1).

We performed autologous stem cell transplantation (SCT) in a pSS patient with lymphocyte interstitial pneumonia (LIP). At the time of diagnosis, the patient's progressive inflammation was poorly controlled by steroid and immunosuppressive drug therapy. Improvements in both pSS and LIP were observed after autologous SCT. We describe this case and review the related literature in this paper.

Case Report

A 32-year-old man visited a local hospital due to fatigue, respiratory distress during exercise, dry eyes, and dry mouth. He was diagnosed with pSS in March 2007. LIP was suspected due to high-resolution computed tomography (HRCT) findings. The patient was treated with prednisolone, hydroxychloroquine, methotrexate, azathioprine, and pilocarpine, without improvement in his symptoms. He was then transferred to our hospital.

The patient was an office worker, and did not have a noteworthy medical or family history. He exhibited a chronically ill appearance. His heartbeat was regular, but his breath sounds revealed crackles in both lung fields. The patient had an oral ulcer. Abnormalities were not found in his abdomen or extremities upon physical examination.

The patient's blood pressure was 120/70 mmHg, his pulse was 78 beats/min, respirations were 20 breaths/min, and body temperature was 36.7°C. In laboratory tests, his white blood

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cell count was 11,900 cells/mm^2 (neutrophils, 86.5%), hemoglobin levels were 10.4 g/dL, and his platelet count was 720,000 cells/mm^2. The patient's erythrocyte sedimentation rate and C-reactive protein levels were elevated at 66 mm/hr and 124.2 mg/L, respectively. In the serum biochemistry test, AST, ALT, BUN, Cr, and electrolytes were all within normal ranges, but protein levels were increased to 10.9 g/dL, and albumin levels were decreased to 2.5 g/dL. Monoclonal gammopathy was not seen in protein electrophoresis. The rheumatoid factor level was 26 mg/dL, the anti-CCP antibody level was normal, the antinuclear antibody titer was 1 : 40 positive with a speckled pattern, the anti-SSA antibody was positive, and the anti-SSB antibody was negative.

The arterial blood gas analysis revealed a pH of 7.469, a pO2 of 73.4 mmHg, a pCO2 of 35.5 mmHg, a HCO3 of 25.2 mmol/L, and an O2 saturation of 95%, and a pulmonary function test showed mild obstructive and restrictive defects with moderately decreased diffusing capacity. In HRCT findings, there were multiple thin-walled cysts located mainly in the upper and middle lung zones and irregularly marginated centrilobular nodules located mainly in the lower lung zone (Figure 1A, B).

Ophthalmologic examination showed bilateral dry eyes and corneal erosions, and mild dermal fibrosis was observed in a lip biopsy (lymphocyte focus score 3). LIP was identified in the results of thoracoscopic open-lung biopsy (Figure 2), and molecular pathology that was performed to rule out lymphoma revealed normal results.

The patient was treated with prednisolone 20 mg qd, hydroxychloroquine 200 mg bid starting in January 2007. His prednisolone dose was increased to 40 mg due to lack of improvement in pneumonia and other symptoms. We then performed cyclophosphamide pulse therapy. From March 2007 to August 2007, the patient was treated with cyclophosphamide 800 mg intravenously each month. After the sixth trial of cyclophosphamide therapy, HRCT showed an increase of lymph node size and extension of the centrilobular nodules. Next, we considered instituting rituximab therapy, but the patient preferred treatment with oral drugs to reduce costs. Therefore, the patient remained ambulatory and was treated with prednisolone, hydroxychloroquine, and azathioprine.

In February 2009, the patient complained of increasing dysp-

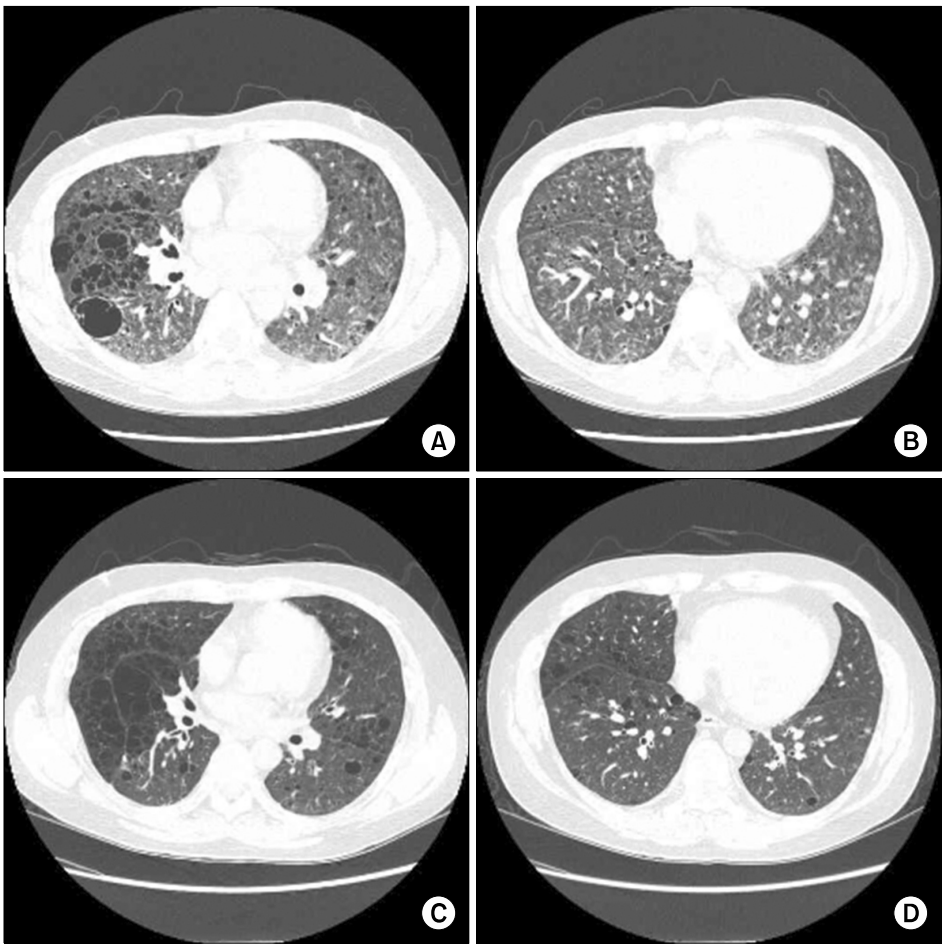

Figure 1. (A) Multiple cysts are found in various sizes on both upper and middle lobes of lung accompanied by multiple lymphadenopathy. (B) Small sized centrilobular nodules are found mainly on both lower lobes of lung. (C) HRCT taken 6 months after auto SCT. Inflammation was improved on both lung field, size and number of lymphadenopathy were all decreased. (D) Both size and number of centrilobular nodules presented on both lung fields were all decreased.

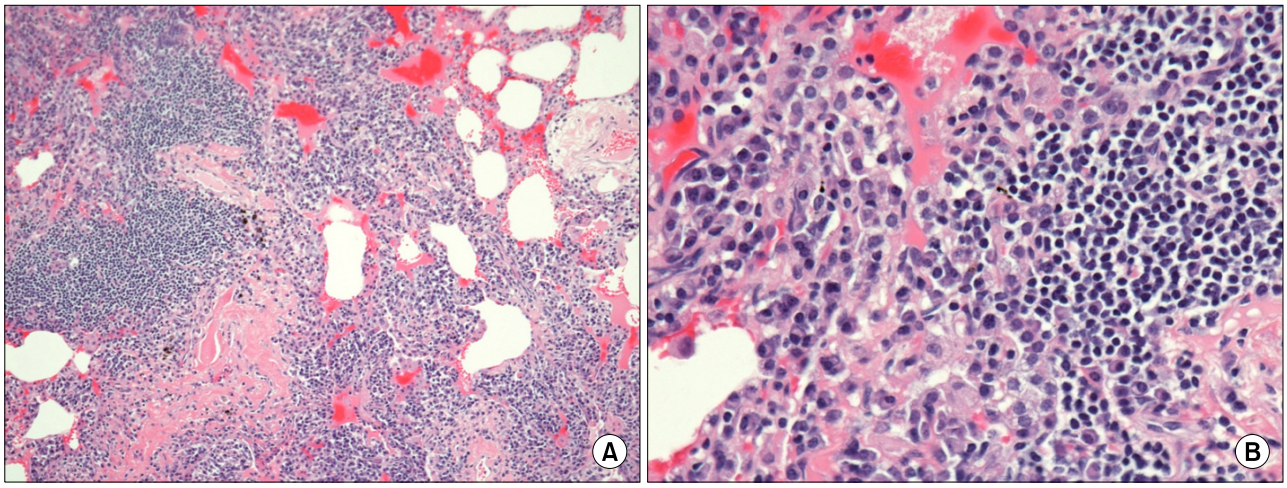

Figure 2. (A) 2×100 (H&E stain), (B) 4×400 (H&E stain). The section shows diffuse interstitial infiltration of lymphoid cells and plasma cells. Scattered small lymphoid follicles are present.

nea on exertion, and increased infiltration of the lung field was revealed on chest radiography. In the laboratory tests, aggravation of anemia (hemoglobin levels of 7.8 g/dL), protein levels of 12.6 g/dL, and albumin levels of 2.0 g/dL were identified. A peripheral blood smear showed a Rouleux formation, while serum IgG, IgA, IgM were all elevated at 6,983 mg/dL, 941 mg/dL, 411 mg/dL, respectively. Serum kappa light chain and lambda light chain levels were also elevated in 7,036 mg/dL and 3,051 mg/dL.

Bone marrow aspiration and biopsy showed that the patient's plasma cells were increased by 11%, but protein electrophoresis showed polyclonal gammopathy, and M protein was not observed. Such polyclonal gammopathy is also observed in inflammatory or infectious conditions, connective tissue disease, and chronic liver disease. In skull X-rays, L-spine MRIs, and pelvic MRIs, no specific osteolytic lesions were observed.

We performed autologous SCT to treat the patient. An induction chemotherapy regimen consisting of vincristine, doxorubicin, and dexamethasone (VAD) was administered 4 times every 3 weeks, and peripheral blood stem cells were collected in October 2009. Peripheral blood stem cell transplantation was performed in November 2009 with high-dose melphalan as the conditioning chemotherapy.

During a follow-up examination conducted 1 year and 6 months after autologous SCT, the patient's pSS symptoms and disease activity were clearly improved. Simultaneously, the centrilobular nodules observed on HRCT were decreased in both number and size, and lymphadenopathy was reduced (Figure 1C, D). Dyspnea on exertion was improved, and the patient's C-reactive protein levels and erythrocyte sedimentation rate were decreased to 10.3 mg/L and 26 mm/hr, respectively. The patient's serial C-reactive protein levels and erythrocyte sedimentation rate levels during the period of treatment are shown in Figure 3. No symptom deterioration or evidence of disease worsening has been observed since treatment, and the patient is now being followed in an outpatient clinic and is receiving a maintenance treatment regimen of low-dose oral prednisolone.

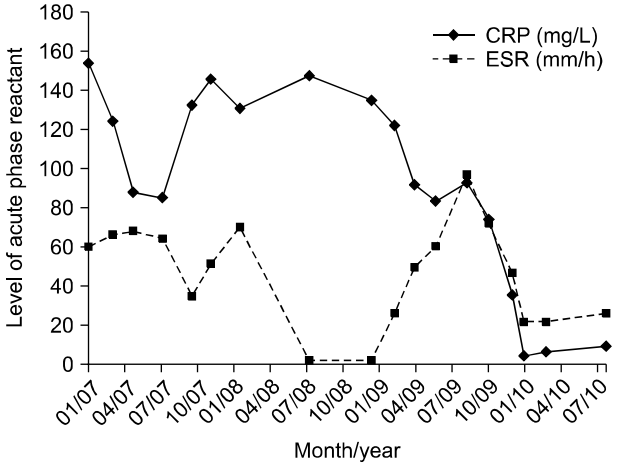

Figure 3. Presented the flow of CRP (mg/L) and ESR (mm/h) during observation periods of the patient. Performed cytoxan pulse therapy from March, 2007 to August, 2007. Performed VAD induction chemotherapy from March, 2009 to June, 2009. Performed autologous SCT in December, 2009.

Discussion

Extraglandular manifestations of pSS are present in 40% to 50% of patients, and result from the lymphocytic infiltration of epithelial tissues. The prevalence of pulmonary involve-

Table 1. Outcome after autologous SCT of Sjögren's syndrome combined with or without hematologic malignancy (6,9-11)

Time, age/sex	Combined disease	Treatment	Outcome
2001, 57/F	NHL	Auto SCT	No change of pSS (remission of NHL)
2006, 57/F	MM	Auto SCT	Recur of pSS (no progression of MM)
2006, 72/F	MM	Auto SCT	Not improvement of pSS (Relapse of MM, died)
2008	None	Auto SCT	90% overall survival rate
10 cases (Oyama et al.)			70% progression free survival rate
34 cases (Nash et al.)			
57 cases (Farge et al.)			

NHL: non Hogkin's lymphoma, MM: multiple myeloma, SCT: stem cell transplantation, pSS: primary Sjögren's syndrome.

ment in pSS is between 9% and 75% (2). The most frequent finding is interstitial lung disease, but lung involvement may occur in a variety forms including xerotrachea, bronchial sicca, obstructive small airway disease, lymphoinfiltrative or lymphoproliferative lung disease, pulmonary hypertension, pleural involvement, lung cysts, and pulmonary amyloidosis (1). In our case, the patient had LIP, in which diffuse infiltration of lymphocytes and plasma cells were observed in the lung biopsy.

The role of lymphocyte infiltration in organs by abnormal memory B cell activity in the pathogenesis of pSS has been investigated. In patients with pSS, peripheral memory $CD27^+$ B cells are reduced (especially $CD27^+IgM^+$ subset), appropriate censoring mechanisms fall in cell cycles, and the incomplete differentiation process increases in ectopic lymphoid tissues. Ectopically formed lymphoid tissues protect autoreactive memory B cells from deletion by normal mechanisms, contribute to the persistence of disease, and in some cases increase the risk of lymphoma (3,4). Thus, disturbance of the immune system and proliferation of immune-related cells are associated with the pathogenesis of pSS.

Treatment of pSS also has been widely investigated due to increases in the available information about its pathogenesis. However, the management of extraglandular manifestations remains mainly empirical. Steroids, immunosuppressive agents, and biological agents (tumor necrosis factor blocker, interferon alpha, B cell depletion therapy) are of some benefit in treatments of systemic manifestation. Anti-B cell therapy (anti-CD20 monoclonal antibody) is currently being investigated for systemic manifestations, and shows promising results, while rituximab is the subject of current large prospective clinical studies (5-7). However, the high incidence of serum sickness-like disorders and infection is a main side effect of rituximab, and therefore remains subject to further evaluation.

Stem cell transplantation has been attempted as an optional treatment for a variety of autoimmune diseases including pSS, systemic lupus erythematosus, and rheumatoid arthritis, but there are no clear criteria in indication for patient screening, treatment regimen, or outcome measurements after transplantation in autoimmune disease (8). However, the relevance of pSS and hematologic malignancy, especially when merged with B cell lymphoma or multiple myeloma, stem cell transplantation was performed as a treatment of lymphoma or multiple myeloma. We searched the literature to investigate outcomes after autologous SCT for primary Sjögren's syndrome combined with or without hematologic malig nancy. These findings are summarized in Table 1. When combined with hematologic malignancy, the improvement of pSS after autologous SCT is not obvious. But without hematologic malignancy, patients with pSS refractory to conventional therapy experience good results after autologous SCT (6,9-11).

There is no standard conditioning regimen for autoimmune disease. VAD regimens are commonly used in multiple myeloma as pre-SCT induction chemotherapy. Plasma cells originate from B cells, grow in bone marrow through malignant transformation and produce abnormal globulins. Multiple myeloma is characterized by monoclonal gammopathy, but not in our case. In multiple myeloma, changes in treatment such as VAD induction therapy and high dose chemotherapy with melphalan followed by SCT significantly increase survival and cure rates (6).

We report a case of a patient with pSS and LIP who exhibited no improvement after previous conventional treatment for pneumonia, and in whom we performed autologous SCT. The activity of the patient's pSS and LIP improved in terms of symptoms, inflammatory markers and HRCT findings. Although autologous SCT is not considered as a first line treatment option in pSS, it could be considered for refractory extraglandular manifestations in pSS.

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