A Case of Lung Involvement Showing Multiple Lung Cysts in Primary Sjögren's Syndrome

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다발성 폐 낭종을 보인 쇼그렌 증후군의 폐 침범 1예

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쇼그렌 증후군은 림프구 침윤과 관련된 만성적인 염증성 자가면역 질환으로 아직 정확한 병태생리학적 기전은 밝혀지지 않았다. 45세 여자 환자가 내원 2년 전 전신 쇠약 및 피로감으로 입원하여 혈청 검사에서 anti- Ro/La antibody 양성, 흉부 단순방사선 및 컴퓨터 촬영에서 양 폐야의 다낭성 병변이 관찰되어 비디오 흉강경을 이용한 폐 생검 시행 결과 세기관지 주위에 림프구 침윤 및 다양한 크기의 폐낭종들이 관찰되어 쇼그렌 증후군의 폐 침범 의심하에 추가 검사 시행하려 하였으나 추적 관찰 되지 않았다. 2년 후 폐렴으로 입원하였으며, 다시 시행한 흉부 컴퓨터 단층촬영에서 다발성 낭성 변화는 큰 차이를 보이지 않았다. 쇼그렌 증후군의 폐 침범은 다양한 형태로 나타나는데, 단순히 세기관지 주위에 림프구 침윤에 의한 다낭성 폐 질환에 대한 보고는 극히 드물다. 따라서 본 저자들은 일차성 쇼그렌 증후군 환자에서 비디오 흉강경을 이용한 폐 생검으로 진단된 세기관지 주위에 림프구 침윤을 동반한 다낭성 폐 질환 1예를 경험하였기에 보고하는 바이다. *(Tuberc Respir Dis 2008;64:230-235)*

Key Words: Sjögren's syndrome, Lung, Cyst, Lymphocyte

Introduction

Sjögren's syndrome, a chronic inflammatory autoimmune exocrinopathy, that is characterized by dry eyes and dry mouth clinically and lymphocytic infiltration of lacrimal and salivary glands pathologically[1]. Lung involvement in Sjögren's syndrome usually consists of lymphocytic infiltration similar to that seen in salivary glands and results in tracheobronchial disease or interstitial lung disease[2,3]. Sjögren's syndrome is associated with various histologic patterns of interstitial lung disease[2,3]. Although there have been earlier reports on lung involvement in Sjögren's syndrome[2,4], there have been few reports on lung involvement with multiple lung cysts caused by only peribronchiolar lymphocytic infiltration in Sjögren's syndrome. We describe herein the first case of Sjögren's syndrome in Korea which presented as multiple cysts caused by only peribronchiolar lymphocytic infiltration and was confirmed by surgical lung biopsy. A brief review of the literature has been included.

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Case Report

Patient: 45-year-old Korean woman

Chief complaints: presented with a 4-week history of dry cough, dyspnea, and dry mouth

Present illness: She was referred to our clinic 2 years ago because of general weakness and fatigue of 2-month duration. Prior to this presentation, she had been admitted to a regional hospital and treated under the clinical diagnosis of pneumonia and anemia. However, she did not improved, so she was referred to our clinic. At that time, she had no obvious pulmonary symptoms. Two years later, she was admitted to our hospital via the

emergency department due to dry cough, dyspnea, and dry mouth of 4-week duration.

Past, family and other history: She had no previous symptoms associated with autoimmune diseases except a history of dry eye for a duration of 6 months. There was neither a family history of autoimmune diseases, nor a history of exposure to drugs or alcohol.

Physical examinations: On physical examination, her blood pressure was 90/60 mmHg, pulse rate 90 beats/min, respiration rate 24/min, and temperature 36.5°C. She had pale conjunctivae and dry tongue, and inspiratory fine crackles were audible in both lower lung fields.

Laboratory findings: Laboratory data on admission showed hemoglobin 8.8 g/dl, hematocrit 29.1%, leukocyte count 3,800/mm^3, platelet count 126,000/mm^3, erythrocyte sedimentation rate (ESR) 60 mm/hr, C-reactive protein (CRP) 194.1 mg/L, serum iron 55 μg/dl (normal, 65～157), total iron binding capacity 217 μg/dl (normal, 250～437), ferritin 78.9 ng/ml (normal, 30～400), aspartate aminotransaminase (AST) 19 IU/L, alanine aminotransaminase (ALT) 8 IU/L, sodium 137 mEq/L, potassium 3.1 mEq/L, chloride 104 mEq/L, total protein 7.3 g/dl, albumin 3.2 g/dl, blood urea nitrogen 9.7 mg/dl, creatinine 1.0 mg/dl, and β_2 microglobulin was 5154.6 ng/ml (normal, 861～1533). Arterial blood gas analysis at room air showed pH 7.416, pCO_2 33.8 mmHg, pO_2 97.2 mmHg, HCO_3^- 21.2 mmHg, and O_2 saturation 97.2%. Serum antinuclear antibody (ANA) positive with a speckled pattern (titer 1:640) and positive for anti- Ro/SS-A (201 IU/ml : 0～10) and La/SS-B (243 IU/ml : 0～15) antibody. However, anti-RNP antibody, anti-smooth muscle antibody, anti-microsomal antibody, anti-Scl 70 antibody, ANCA, and anti-ds antibody were negative.

Serum C_3 and C_4 were 91.4 mg/dl (normal, 90～180) and 27.0 mg/dl (normal, 10～40), respectively. The serum immunoglobulin (Ig) showed IgG 1686.9 mg/dl (normal, 700～1600), IgA 201.7 mg/dl (normal, 70～400), and IgM 113.1 mg/dl (normal, 40～230). Serum and urine electrophoresis and immunoelectrophoresis showed unremarkable findings except that urine electrophoresis demonstrated a polyclonal pattern with increased amount of α_1 and γ globulins. The Schirmer test showed 4/4 (right/left) mm/5 min (normal, >5/5 mm/5 min), which was suggestive of decreased lacrimation. Pulmonary function tests (PFT) showed decreased forced vital capacity (FVC) 2.30 L (67% predicted normal), forced expiratory volume in 1 second (FEV1) 1.80 L (66% predicted normal), FEV1/FVC 78%, forced expiratory flow $(FEF)_{25\sim75}$ 1.64L (59% predicted normal), and diffusing lung capacity of carbon monoxide (DL_{CO}) 10.29 ml/min/mmHg (46% predicted normal), which indicated mild restrictive impairment combined with small airways obstructive disease.

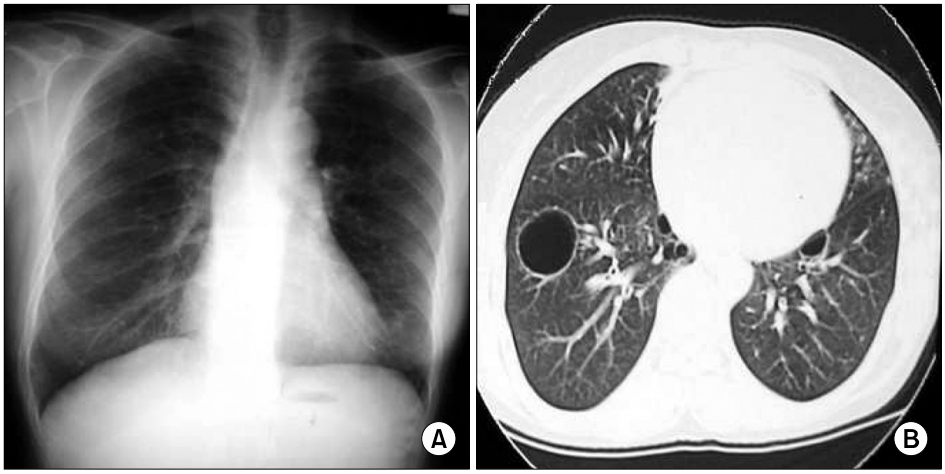

Figure 1. Chest radiographs and computed tomography at initial visit. (A) Chest radiographs showing bilateral multiple cysts, and (B) chest CT showing multiple well-demarcated, variable-sized cystic lesions in both lung fields.

Radiologic findings: Chest radiographs and computed tomography (CT) showed multiple well-demarcated variable-sized cystic lesions in both lung fields (Figure 1). Two years later, chest radiographs showed multiple cystic lesions in both lung fields combined with pneumonic infiltration in both lower lungs. When compared with a prior chest CT, chest CT demonstrated multiple cystic lesions in both lung fields without any interval changes except some consolidations in both lower lung fields with bronchovascular bundle thickening (Figure 2).

Histopathologic findings: Bronchoscopy was performed with transbronchial lung biopsy (TBLB). Bronchofibroscopy showed no endobronchial lesions, and the specimen taken from the right posterior basal segment by TBLB exhibited mild interstitial thickening and mild infiltration of chronic inflammatory cells. Five days after bronchoscopy, lung biopsy was performed using video-assisted thoracic surgery (VATS). Microscopically, the resected lung specimen revealed multifocal, various-sized cysts and peribronchiolar lymphocytic infiltration without any atypism, but the other parenchymal tissue showed no abnormal findings (Figure 3), which was

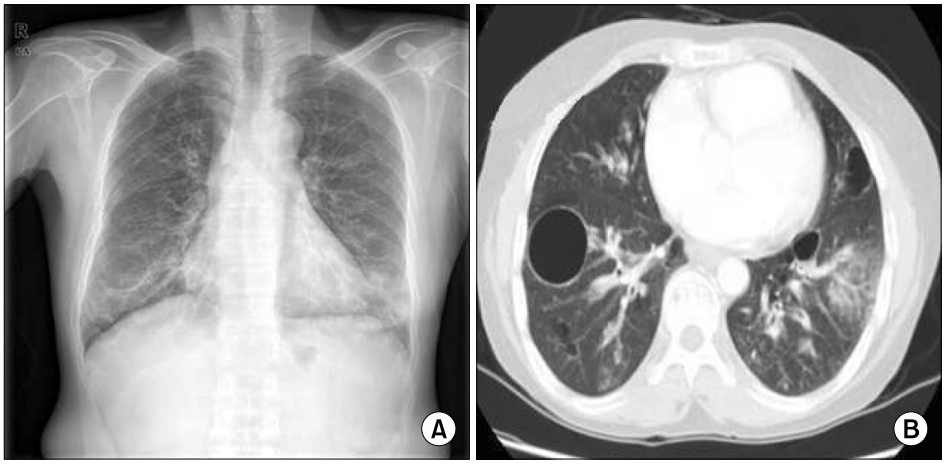

Figure 2. Chest radiographs and computed tomography at second time visit. (A) Chest radiographs showing multiple cystic lesions combined with pneumonic infiltration in both lower lungs, and (B) chest CT showing multiple cystic lesion of variable-size and some consolidations in both lower lungs with bronchovascular bundle thickening.

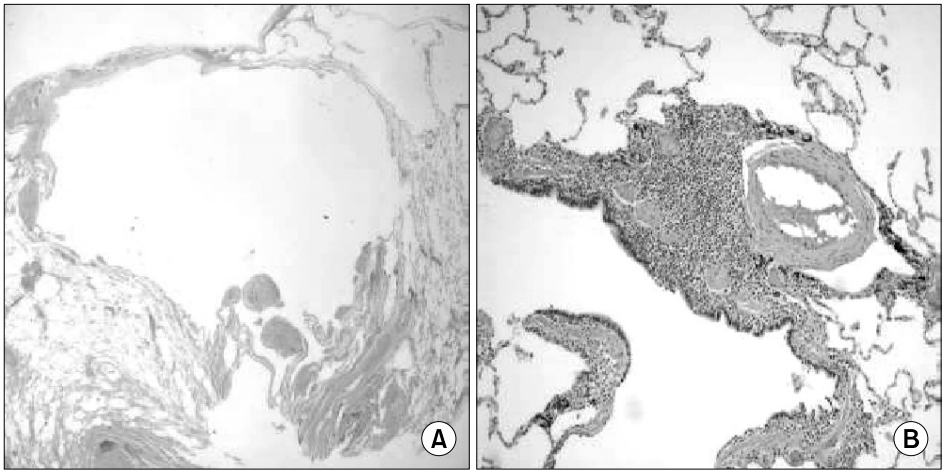

Figure 3. Histologic finding of wedge resected lung specimen. (A) Small cyst is noted (H&E stain, ×10). (B) Peribronchiolar lymphocytic infiltration without atypism is revealed (H&E stain, ×100).

consistent with lung involvement in Sjögren's syndrome.

Clinical course and treatment: Two years ago when the patient was suspected to have Sjögren's syndrome with lung, we planned further workup including ophthalmoloic evaluation, but she was lost to follow-up after being discharged from the hospital. At the second admission, she received 4 boluses of intravenous methyprednisolone (62.5 mg daily), followed by oral prednisolone (0.5 mg/kg/day) with intravenous antibiotics. Ten days later, she improved and was discharged from the hospital with oral prednisolone (0.5 mg/kg/day) and oral antibiotics. One month later, dosage of oral prednisolone was tapered to 0.2 mg/kg/day. She has been followed up regularly without any significant interval change of multiple lung cysts on chest radiographs.

Discussion

Sjögren's syndrome is a slowly progressive chronic autoimmune disorder of the exocrine glands with associated lymphocytic infiltrates, which exhibits a wide range of organ-specific and systemic extraglandular manifestations including lung involvement[1,3]. Despite extensive studies of the underlying causes of Sjögren's syndrome, the pathogenesis remains obscure[1]. The syndrome can be seen alone (primary Sjögren's syndrome) with a prevalence of about 0.5% to 3% or in association with other autoimmune diseases (secondary Sjögren's syndrome)[3]. Primary Sjögren's syndrome mainly affects women with a female-to-male ratio of 9 : 1, and may occur in patients at all ages, but it typically has its onset in the fourth to the sixth decades[1,3].

Patients with Sjögren's syndrome have symptoms related to diminished lacrimal and salivary gland function and frequently present with xerostomia, keratoconjunctivitis sicca, and parotid gland enlargement. Although it is commonly observed, pulmonary involvement is seldom clinically significant in patients with Sjögren's syndrome. Dry cough is often the main respiratory symptom and is usually a manifestation of xerotrachea[3]. The reported frequency of pulmonary involvement in primary Sjögren's syndrome varies widely, ranging from 9% to 75% depending on the detection method employed. Also, primary Sjögren's syndrome is manifested as various forms of small airway and interstitial lung diseases[2,4]. Ito et al[5] reported that 33 patients with primary Sjögren's syndrome associated interstitial lung disease (ILD) and that nonspecific interstitial pneumonia (NSIP) was the most common histopathologic pattern, occurring in 61% of patients. Lymphocytic interstitial pneumonia (LIP) is a benign polyclonal proliferation, usually of mature B cells, that is either multifocal or diffusely involves the lungs. Histologically, LIP is characterized by massive interstitial lymphoid infiltrates predominately basilar membrane and diffusely spreading into the alveolar septa, although there may occasionally be some sparing of the lungs[6].

Different kinds of PFT have been reported in many studies. Segal et al[7] reported obstructive disease was detected in 37% of patients with Sjögren's syndrome, while Constrantopoulos et al[8] found small airway disease in 22% of patients with Sjögren's syndrome. In the study of Newball and Brahim[9], 46% of patients with Sjögren's syndrome showed obstructive disease. However, most studies reported higher incidences of restrictive disease[2,5]. Small airway narrowing and obstructive lung disease are thought to be related to peribronchiolar lymphocytic infiltration[10,11]. Airway narrowing due to peribronchiolar mononuclear cell infiltration causes a check-valve mechanism, which may lead to cyst formation[11,12]. The $FEF_{25\sim75}$ is often considered a more sensitive measurement of early airflow obstruction, particularly in the small airways. However, this measurement must be cautiously interpreted because it is less reproducible[10].

Although pulmonary involvement associated with Sjögren's syndrome has attracted attention recently, cyst formation has been rarely reported. Cyst formation, a rare pulmonary manifestation in Sjögren's syndrome, has been reported to be mainly associated with LIP. Cysts with only peribronchiolar lymphocytic infiltration but without LIP features have rarely been reported. From a review of the literature, only 8 cases were found around the world[11-13]. Compared with these cases, the

bronchiole were severely involved by dense lymphocytic infiltrates in our case, but the interstitium of the alveoli were almost intact. Histologic findings of these reported cases showed lymphocytic infiltration through the interstitial space of the alveoli and a widening of the alveolar septa, whereas those of our case favor peribronchiolar lymphocytic involvement of Sjögren's syndrome with multiple cysts than LIP associated with Sjögren's syndrome.

Until recently, there have been several sets of diagnostic criteria for Primary Sjögren's syndrome[1,3]. Although minor salivary gland traditionally has been traditionally considered the "gold standard" for the diagnosis of Sjögren's syndrome, newer criteria permit classification of Sjögren's syndrome without necessarily performing this procedure. An American-European consensus committee recently modified and reapproved the criteria. These criteria encompass the presence of subjective and objective sicca manifestations, antibodies to Ro/SS-A and La/SS-B, and characteristic histopathologic findings in minor salivary glands[3]. Our case was diagnosed as Sjögren's syndrome based on ocular and oral sicca symptoms, positive Schirmer test, and positive antibodies to anti- Ro/SS-A and La/SS-B.

Treatment of Sjögren's syndrome is mainly symptomatic and is directed toward early diagnosis and treatment of its complications[3]. Topical agents have been used for improving moisture and decreaseing inflammation. Systemic treatment includes steroidal and nonsteroidal anti-inflammatory agents, disease-modifying agents, and cytotoxic agents to address the extraglandular manifestations involving the skin, lung, heart, kidney, and nervous systems[1].

The 5-year survival rate of Sjögren's syndrome with lung involvement was reported to be 84%. The causes of death were as follows; malignant lymphoma, NSIP, Aspergillus infection and gastrointestinal bleeding during corticosteroid therapy. Some of the studies showed an association between mortality and baseline PaO_2[5]. Theander et al[14] did not find an increase of mortality in patients with lung involvement of Sjögren's syndrome compared with the general population. Kruize et al[15] reported that a long-term follow-up (10 to 12 years) of 29 patients with primary Sjögren's syndrome showed a mild and stable course of glandular and extraglandular manifestations and that none of them developed clinically significant pulmonary diseases. Although Sjögren's syndrome is a benign and non-life threatening disorder, patients should be managed with appropriate treatment in order to improve quality of life and to avoid complications. However, optimal treatment for patients with Sjögren's syndrome-associated specific disease remains to be defined[2].

Summary

We described herein the first case of primary Sjögren's syndrome in Korea which presented with multiple cysts caused by only peribronchiolar lymphocytic infiltration, a rare pulmonary manifestation in Sjögren's syndrome, and was confirmed by surgical lung biopsy. A brief review of the literature has been included.

References

1. Fox RI. Sjögren's syndrome. Lancet 2005;366:321-31.
2. Parambil JG, Myers JL, Lindell RM, Matteson EL, Ryu JH. Interstitial lung disease in primary Sjögren syndrome. Chest 2006;130:1489-95.
3. Kassan SS, Moutsopoulos HM. Clinical manifestations and early diagnosis of Sjögren syndrome. Arch Intern Med 2004;164:1275-84.
4. Jang DY, Shin BC, Jung KY, Kim JO, Yang JT, Joo YC, et al. A case of Sjögren's syndrome with interstitial lung disease and multiple cystic disease. Tuberc Respir Dis 2001;51:597-602.
5. Ito I, Nagai S, Kitaichi M, Nicholson AG, Johkoh T, Noma S, et al. Pulmonary manifestations of primary Sjögren's syndrome: a clinical, radiologic, and pathologic study. Am J Respir Crit Care Med 2005;171:632-8.
6. Travis WD, Colby TV, Koss MN. Rosado-de-Christenson ML, Müler NL, King Jr TE. Non-neoplastic disorders of the lower respiratory tract. 2nd ed. Washington, DC: American Registry of Pathology; 2002. p. 265-77.
7. Segal I, Fink G, Machtey I, Gura V, Spitzer SA. Pulmonary function abnormalities in Sjögren's syndrome and the sicca complex. Thorax 1981;36:286-9.
8. Constantopoulos SH, Papadimitriou CS, Moutsopoulos

HM. Respiratory manifestations in primary Sjögren's syndrome. A clinical, functional, and histologic study. Chest 1985;88:226-9.
9. Newball HH, Brahim SA. Chronic obstructive airway disease in patients with Sjögren's syndrome. Am Rev Respir Dis 1977;115:295-304.
10. Papiris SA, Maniati M, Constantopoulos SH, Roussos C, Moutsopoulos HM, Skopouli FN. Lung involvement in primary Sjögren's syndrome is mainly related to the small airway disease. Ann Rheum Dis 1999;58:61-4.
11. Sakamoto O, Saita N, Ando M, Kohrogi H, Suga M, Ando M. Two cases of Sjögren's syndrome with multiple bullae. Intern Med 2002;41:124-8.
12. Kobayashi H, Matsuoka R, Kitamura S, Tsunoda N, Saito K. Sjögren's syndrome with multiple bullae and pulmonary nodular amyloidosis. Chest 1988;94:438-40.
13. Gardiner P, Ward C, Allison A, Ashcroft T, Simpson W, Walters H, et al. Pleuropulmonary abnormalities in primary Sjögren's syndrome. J Rheumatol 1993;20:831-7.
14. Theander E, Manthorpe R, Jacobsson LT. Mortality and causes of death in primary Sjögren's syndrome: a prospective cohort study. Arthritis Rheum 2004;50:1262-9.
15. Kruize AA, Hene RJ, van der Heide A, Bodeutsch C, de Wilde PC, van Bijsterveld OP, et al. Long-term follow up of patients with Sjögren's syndrome. Arthritis Rheum 1996;39:297-303.