

CASE REPORT

Primary Sjogren's syndrome complicated by bilateral pleural effusion

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Abstract: Sjogren's syndrome can cause many organic changes, but is rarely accompanied by pleuritis. We report a 65-year-old patient with primary Sjogren's syndrome who developed bilateral pleuritis with moderately large effusions. He was diagnosed as having Sjogren's syndrome, based on xerophthalmia, xerostomia, positive results for anti-Sjogren's syndrome (anti-SS-A/SS-B) antibodies, the Schirmer test and biopsy findings in the minor salivary glands. The pleural fluid was lymphocyte rich and contained high levels of anti-SS-A/SS-B antibodies. There was no evidence of infection, malignancy or other collagen diseases which cause pleuritis. We conclude that this case adds to the eight previously published reports of primary Sjogren's syndrome complicated by pleural effusion.

Key words: anti-SS-A/SS-B antibodies, pleural effusion, pleuritis, Sjogren's syndrome.

INTRODUCTION

Sjogren's syndrome is a systemic autoimmune disease that is characterized by sicca symptoms.^{1,2} Many organic changes have been reported in patients with Sjogren's syndrome.^{1,2} Interstitial pulmonary fibrosis and tracheobronchial sicca are the most common presentation of pulmonary involvement in primary Sjogren's syndrome.³ However, it is rarely accompanied by serositis such as pleuritis or pericarditis.³ There have only been eight previous reports of primary Sjogren's syndrome complicated by pleural effusion.^{3–9} As a result, little is known about the relationship between Sjogren's syndrome and pleural effusion.^{4,10} We report a 65-year-old man with primary

Sjogren's syndrome who developed bilateral pleuritis with moderate effusions.

CASE REPORT

A 65-year-old man was admitted to the Department of Internal Medicine, Kiryu Kousei General Hospital in February 2004, because of cough and dyspnoea. A CXR showed bilateral pleural effusions. When examining the patient in order to make a diagnosis, the amount of effusion increased and the symptoms of dyspnoea worsened. Although the cause of the pleural effusion was unclear, infection was ruled out and an empirical trial of prednisolone (30 mg/day orally) was started, because of the worsening effusion and dyspnoea of the patient. There was no immediate effect of the prednisolone treatment. Therefore, a right-side pleurodesis was performed, after which the pleural effusion increased on the left side. Corticosteroid treatment was initiated, with pulse administration of methylprednisolone (500 mg/day, for 3 days) followed by prednisolone (60 mg/day), and brought about dramatic improvement of the pleural effusion. The daily prednisolone dose was gradually reduced from 60 mg to 15 mg over 13 weeks. However, the

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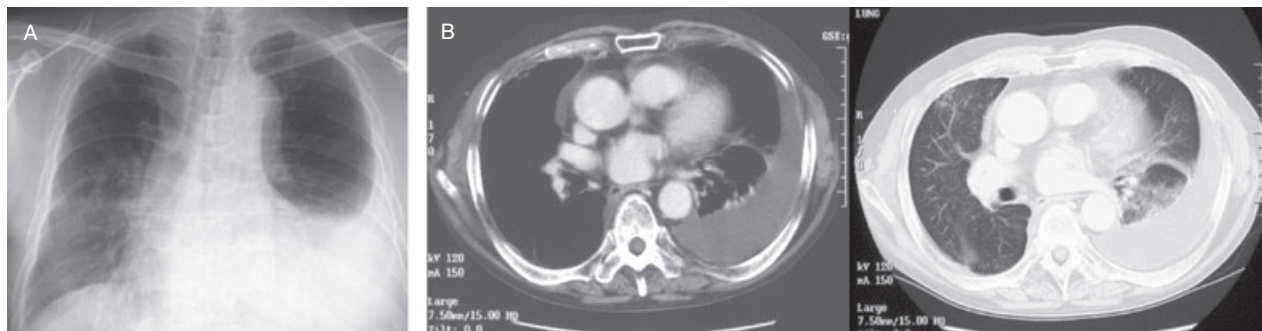


Figure 1 (A) CXR on admission to hospital showed a left-side effusion after right-side pleurodesis; (B) A chest CT scan on admission to hospital (after right-side pleurodesis) also revealed a left-side pleural effusion, but there was no abnormality in the lung parenchyma.

pleural effusion increased again after reduction of the prednisolone dose to 15 mg/day. Therefore, the patient was transferred to Gunma University Hospital for a precise diagnosis and further treatment. The patient had received a total of 4410 mg of prednisolone before transfer to our hospital.

The patient's past history was unremarkable, except for hypertension and a desmoid tumour resection. There was no history of smoking and his family history was unremarkable. A physical examination revealed reduced air entry on the left side. He described symptoms of xerophthalmia and xerostomia. However, no skin or mucosal lesions, or joint disorders were observed. A CXR (Fig. 1A) and CT (Fig. 1B) revealed the left-side pleural effusion, but there was no abnormal lesion in the lung parenchyma.

The laboratory findings on the first admission to Kiryu Kosei General Hospital were as follows: normal urinalysis, WCC $4.8 \times 10^9/L$, Hb 130 g/L and platelet count $268 \times 10^9/L$. Biochemical analyses were unremarkable except for albumin 30 g/L, CRP 14 g/L and ESR 88 mm/h. Tests for lupus erythematosus and rheumatoid factor (RF) were negative. Antinuclear antibody titre was positive at 1:320, but the anti-DNA antibody test was negative. Tests for antibodies to extractable nuclear antigens, nRNP, centromere and Sm were all negative. Anti-SS-A antibody and anti-SS-B antibody levels were >500 and 49.0 U/mL, respectively (normal <10 U/mL). Tests for myeloperoxidase-antineutrophil antibody (ANCA) and proteinase-3-ANCA were negative. Tests for tumour markers were negative, except for soluble IL-2 receptor, which was 1680 U/mL. Serological tests for cytomegalovirus, herpes simplex virus, Epstein-Barr virus and mycoplasma were negative. The purified protein derivative of tuberculin skin test was positive (11 mm) but this had to be interpreted with the past history of BCG vaccination. Pleurocentesis was performed and revealed that the pleural fluid was an exudate. No malignant cells were detected in the effusion, but many lymphocytes were present. The pleural fluid total leukocyte count was $1.52 \times 10^9/L$ (neutrophils 2.0%, eosinophils 0.0%, lymphocytes 84.0%). There was no monoclonality of the lymphocytes based on a flow cytometric analysis. The smear test findings for *Mycobacterium tuberculosis* and bacterial

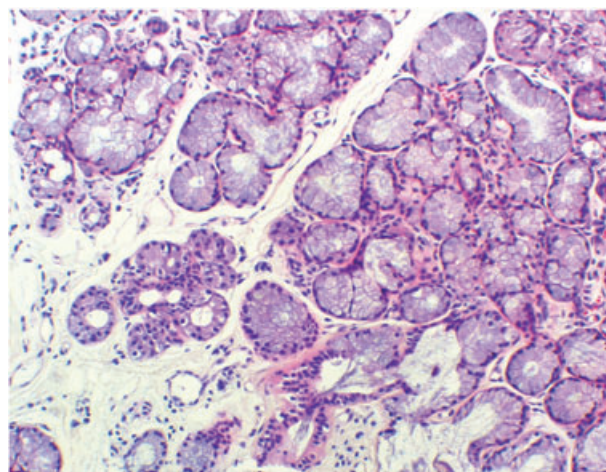


Figure 2 A lip biopsy specimen revealed atrophy of the salivary gland and mild lymphocytic infiltration around the salivary gland ducts (haematoxylin and eosin stain).

culture were negative. A PCR examination for *M. tuberculosis* was also negative. The antinuclear antibody titre of the pleural fluid was 1:80. Anti-SS-A antibody and anti-SS-B antibody levels in the pleural effusion were 89.9 and 34.3 U/mL, respectively. RF and hyaluronic acid was negative. BAL fluid taken from the right lung contained 2.8×10^5 cells/mL (neutrophils 2%, lymphocytes 72%, alveolar macrophages 26%).

An ophthalmological examination revealed a positive Schirmer test, and a lip biopsy specimen (Fig. 2) showed atrophy of the salivary gland and mild lymphocytic infiltration around the salivary gland ducts. Because the lip biopsy was performed after administration of prednisolone, the lymphocyte infiltration may have been under-estimated. We therefore diagnosed Sjogren's syndrome based on xerophthalmia, xerostomia, a positive finding for anti-SS-A/SS-B antibodies, the Schirmer test, and biopsy findings. There was no evidence that the patient had any other collagen diseases that could cause pleuritis.

Gallium scintigraphy and 18F-FDG-PET showed no abnormal uptake. However, a pleural biopsy showed

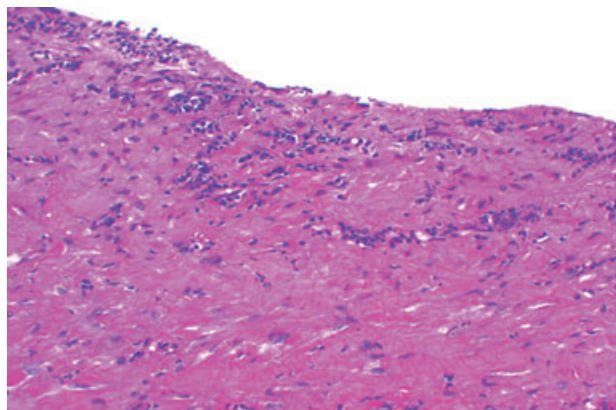


Figure 3 A pleural biopsy specimen shows fibrous changes and infiltration of lymphocytes.

lymphocyte infiltration but malignant lymphoma could not be entirely excluded. Hence, thoracoscopy was performed and the thoracoscopic pleural biopsy (Fig. 3) showed a marked infiltration of lymphocytes with no evidence of lymphoma or malignant mesothelioma. There was no evidence of *M. tuberculosis* in the histological examination or from the culture of pleural biopsy specimens obtained during thoracoscopy. The pleural effusion improved after increasing the prednisolone dose. After 2 years of follow up, there was no evidence of coexisting autoimmune disease and the pleural effusion was well controlled with daily administration of 3 mg of prednisolone.

DISCUSSION

Sjogren's syndrome is a systemic autoimmune disease characterized by sicca symptoms.^{1,2} Cases complicated by other collagen disorders such as rheumatoid arthritis, systemic lupus erythematosus (SLE), and scleroderma are classified as secondary Sjogren's syndrome.³ Interstitial pulmonary fibrosis and tracheobronchial sicca are the most common symptoms of pulmonary involvement in primary Sjogren's syndrome.³ Some cases are also complicated by pulmonary arterial hypertension, pseudolymphoma, pulmonary lymphoma, lymphocytic interstitial pneumonitis and amyloidosis.¹¹ However, this disease is rarely accompanied by serositis such as pleuritis or pericarditis.³ There have been only eight reports of primary Sjogren's syndrome complicated by pleural effusion (Table 1). Miyawaki *et al.*¹³ reported that 42 of 88 cases (47.7%) of Sjogren's syndrome were complicated by pulmonary lesions. However, only one case of secondary Sjogren's syndrome complicated by SLE had a pleural effusion.¹³ Papatnasiou *et al.*¹⁴ reported that pleural effusion was not observed in 40 cases of primary Sjogren's syndrome, although it was observed in two of 26 cases (8%) of secondary Sjogren's syndrome.

In the present patient, there was no evidence of infective or malignant causes for the development of

Table 1 Previous reports of primary Sjogren's syndrome complicated by pleural effusion

Case	Authors	Year	Age (years)	Gender	Chief symptoms	ANA		Anti-SS-A		Anti-SS-B		Cells
						Serum	Pleural effusion	Serum	Pleural effusion	Serum	Pleural effusion	
1	Alvarez-Sala <i>et al.</i> ⁴	1989	64	F	Chest pain	+	ND	-	ND	+	ND	Lymphocytes
2	Kashiwabara <i>et al.</i> ⁵	1995	40	F	Fever	1:80	ND	1:64	ND	1:8	ND	Lymphocytes
3	Ogihara <i>et al.</i> ³	1995	62	M	Fever	1:40	ND	1:4	1:4	1:8	1:8	Lymphocytes
4	Inoue <i>et al.</i> ¹²	1996	73	F	Dyspnoea	1:160	ND	-	-	-	-	Lymphocytes
5	Suzuki <i>et al.</i> ⁶	1996	53	F	Cough	1:160	1:80	+	ND	+	ND	ND
6	Kawamata <i>et al.</i> ⁷	1997	70	M	Cough	1:1280	ND	+	+	-	-	Lymphocytes
7	Tanaka <i>et al.</i> ⁸	2000	45	F	Fever	1:320	1:320	1:16	1:16	1:8	1:4	Lymphocytes
8	Horita <i>et al.</i> ⁹	2000	73	M	Dyspnoea	1:320	ND	25.9 U/mL	22.3 U/mL	59.1 U/mL	76.4 U/mL	Lymphocytes
9	Present case	2006	65	M	Cough, dyspnoea	1:320	1:80	>500 U/mL	89.9 U/mL	49 U/mL	34.3 U/mL	Lymphocytes

F, female; M, male; ND, Not determined.

the effusion. Other autoimmune disorders that cause pleuritis, such as SLE, were also ruled out. We therefore concluded that the pleural effusion was associated with primary Sjogren's syndrome.

The pleural fluid from the present patient showed increased numbers of lymphocytes and elevated levels of SS-A/SS-B antibodies. Kawamata *et al.*⁷ reported that the titres of RF, SS-A antibody and immune complexes were higher in pleural effusion in comparison with their respective serum levels in patients with pleural effusions associated with primary Sjogren's syndrome. On the other hand, complement levels were lower in pleural effusion in comparison with their serum concentrations. They suggested that immune responses such as production of auto-antibody and immune complexes, and activation of the complement cascade could occur in the pleural cavity.⁷

However, in the present case, a definite diagnosis of Sjogren's syndrome as the aetiology of the pleural effusion could not be made as there is no specific test that can be used for this purpose. Pleural involvement in patients with primary Sjogren's syndrome is so rare that there remains a concern that the pleural effusions described may actually be due to coexisting conditions. A coexisting autoimmune disease such as SLE or rheumatoid arthritis should first be considered. Patients require close and careful follow up to identify the development of any overt autoimmune disease. Further studies will be necessary to confirm the incidence and mechanism of the association between primary Sjogren's syndrome and pleural effusion. In conclusion, the possibility that pleuritis may be associated with Sjogren's syndrome, although rare, should be considered.

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