

[CASE REPORT]

Sjögren's Syndrome with Pleural Effusion: Difficult to Distinguish from Tuberculous Pleurisy Because of a High Adenosine Deaminase Level

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Abstract:

An 84-year-old woman visited our hospital for dyspnea due to right pleural effusion, with lymphocytic dominance and a high adenosine deaminase (ADA) level, that had been noted 1 month earlier. She was suspected of having tuberculous pleurisy; however, anti-tuberculosis treatment yielded no improvements. She was diagnosed with pleural effusion due to primary Sjögren's syndrome (SjS) based on her dry eyes and mouth, positivity for anti-Sjögren's-syndrome-related antigen A/B, and histopathologic findings of a lip biopsy and thoracoscopic pleural biopsy. Her symptoms improved after starting steroid therapy. Cases of pleural effusion due to SjS with a high ADA level may be misdiagnosed as tuberculous pleurisy.

Key words: Sjögren's syndrome, pleural effusion, adenosine deaminase, tuberculous pleurisy

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Introduction

Primary Sjögren's syndrome (SjS) is a chronic autoimmune disorder of the exocrine glands with associated lymphocytic infiltration of the affected glands; SjS is a rare disease, with a prevalence in the general population of approximately 0.5% (1).

Pleural effusion is very rare in SjS patients, with an incidence of less than 1% (2). Some studies on pulmonary manifestations of primary SjS have not reported pleural effusion (2), and a previous report stated that only 2 of 343 patients with primary SjS had pleural effusion (3). Generally, pleural effusion in patients with SjS is exudative with lymphocytic dominance, a high concentration of anti-Sjögren's syndrome-related antigen A (SS-A)/anti-Sjögren's syndrome-related antigen B (SS-B), low complement levels, and usually low adenosine deaminase (ADA) levels (4); the relationship between SjS and pleural effusion is uncertain (2, 5). The level of ADA in the pleural fluid is gener-

ally used as a marker for a diagnosis of tuberculous pleurisy (6, 7).

We herein report a rare case of SjS with high ADA levels in the pleural effusion that was distinguished from tuberculous pleurisy based on a thoracoscopic pleural biopsy.

Case Report

We encountered an 84-year-old woman who had developed dyspnea 1 month earlier. She had a medical history of bronchial asthma, eosinophilic pneumonia, and diabetes mellitus. She had no smoking history and no relevant allergic history. She visited a local doctor due to dyspnea, and radiography showed the presence of right pleural effusion. Thoracentesis revealed that her pleural effusion was exudative with lymphocytic dominance and high ADA levels of 52 U/L; therefore, she was suspected of having tuberculous pleurisy and visited our hospital.

Her vital signs were normal, although she had a low-grade fever of 37.3 °C. A physical examination revealed de-

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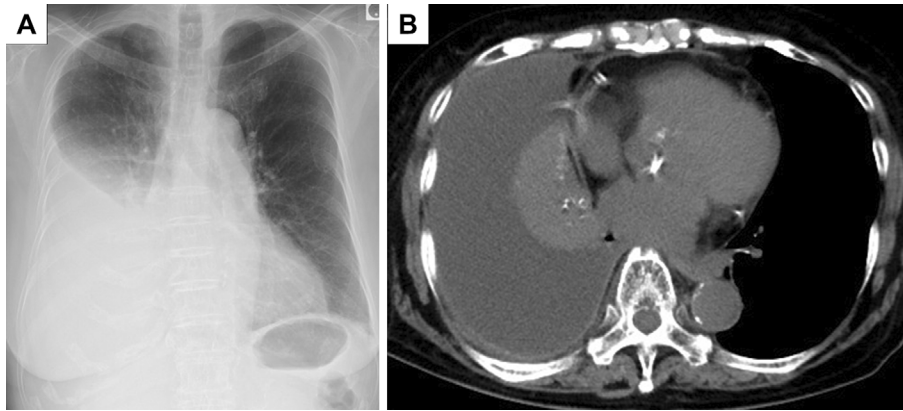


Figure 1. Chest radiography and computed tomography showed a large amount of right pleural effusion without a lung lesion.

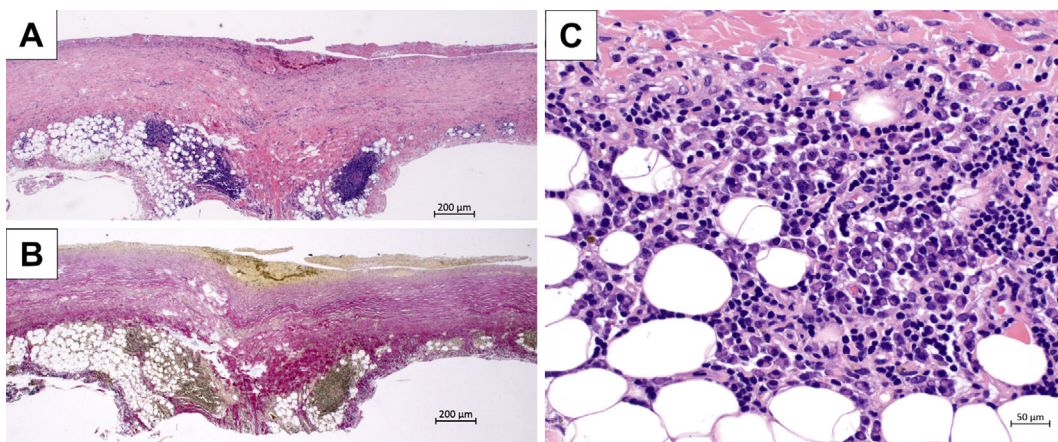


Figure 2. A thoracoscopic pleural biopsy revealed pleural fibrotic thickening with marked infiltration of lymphocytes, without evidence of granuloma formation or malignancy. A: Hematoxylin and Eosin (H&E) staining $\times 50$. B: Elastica van Gieson staining $\times 50$. C: H&E staining $\times 200$.

creased breath sounds in the right lower lung, dry eye, and dry mouth. Laboratory findings were as follows: white blood cell count of 4,620 cells/ μL , with 81.0% polymorphic nuclear leukocytes; C-reactive protein level of 3.94 mg/dL; hemoglobin A1c level of 8.4%; antinuclear antibody (ANA) 1:160 dilution with speckled immunofluorescence pattern; anti-SS-A antibody level $>1,200.0$ U/mL; and anti-SS-B antibody level of 563.0 U/mL. Her serum IgG and IgG4 levels were 2,651 mg/dL and 39.4 mg/dL, respectively. Anticyclic citrullinated peptide antibody and an interferon gamma release assay (IGRA) showed negative results.

Chest radiography and computed tomography (CT) showed a large amount of right pleural effusion without a lung lesion (Fig. 1). The pleural effusion obtained by thoracentesis showed lymphocyte dominance (78.0%), a total protein (TP) level of 5.88 g/dL, a lactate dehydrogenase (LDH) level of 230 IU/dL, a glucose level of 131 mg/dL, and an ADA level of 45.1 U/L. Pleural fluid bacterial culture, tuberculosis examinations [smear and polymerase chain reaction (PCR) tests], and cytology were negative.

She was suspected of having tuberculous pleurisy due to her high ADA levels and was started on empiric therapy

with antituberculosis medicine (isoniazid, rifampicin, ethambutol, and pyrazinamide). However, her symptoms and pleural effusion did not improve after over two months of treatment. Additional examinations of the pleural effusion showed ANA at a 1:160 dilution with a speckled immunofluorescence pattern, an anti-SS-A antibody level $>1,200.0$ U/mL, and an anti-SS-B antibody level of 656.0 U/mL. The pleural fluid IgG level was 1,965 mg/dL, and the IgG4 level was 21.0 mg/dL. The complement component levels in the pleural effusion (C3 41 mg/dL, C4 5 mg/dL, and total complement <12.0 U/mL) were lower than in the serum (C3 128 mg/dL, C4 16 mg/dL, and total complement 45.9 U/mL).

We performed a thoracoscopic pleural biopsy, which revealed pleural fibrotic thickening with marked infiltration of lymphocytes and no evidence of granuloma formation or malignancy (Fig. 2). Immunohistochemical staining showed few IgG4-positive cells and an IgG4/IgG ratio $<25\%$. In addition, an ophthalmological examination showed a positive Schirmer's test (right eye 0 mm, left eye 0 mm), and keratoconjunctivitis sicca was observed. The GAM test showed reduced salivary flow (3.5 mL/10 minutes). A histopathologic

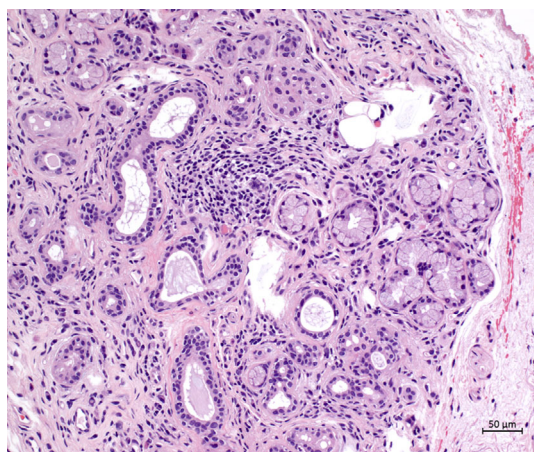


Figure 3. A histopathologic examination of the lip biopsy showed lymphocyte infiltration around the salivary gland ducts.

examination of the lip biopsy showed lymphocyte infiltration around the salivary gland ducts (Fig. 3). Accordingly, she met the diagnostic criteria for and was diagnosed with pleural effusion due to primary SjS (1).

Her symptoms, laboratory findings and radiographic findings gradually improved after starting treatment with 20 mg of prednisolone. The prednisolone dose was gradually reduced to 9 mg over the course of 6 months, and there has been no evidence of recurrence thus far. We obtained informed consent from the patient for the publication of this report.

Discussion

We herein report a case of primary SjS with pleural effusion, characterized by lymphocytic dominance, exudation, and a high concentration of ADA. It was difficult to rule out tuberculous pleurisy; therefore, we performed a thoracoscopic pleural biopsy. The anti-SS-A and anti-SS-B levels in the pleural effusion were elevated, similar to the serum data. Her symptoms, laboratory findings, and radiographic findings improved with steroid therapy.

Generally, SjS patients with pleural effusion show lymphocytic dominance and exudation with normal glucose levels and pH and low pleural fluid ADA levels (2). ADA is an enzyme produced by the lymphocytes that participates in purine catabolism in the pathway from adenosine to inosine (6). Elevated levels of ADA in the pleural fluid are a useful marker for the diagnosis of tuberculous pleurisy (6, 7), and the most widely accepted cut-off value for ADA in the pleural fluid for the diagnosis of tuberculous pleurisy is 40 U/L, with a sensitivity and specificity of 92% and 90%, respectively (7). Therefore, in our patient, tuberculous pleurisy could not be ruled out initially, and empiric therapy with antituberculosis medicine and a thoracoscopic pleural biopsy were needed.

There have been 12 other case reports of primary SjS with pleural effusion, which are shown in Table (5, 8-18).

Five of the 13 total reports, including our study, described the pleural fluid ADA levels, and 3 patients had high ADA levels of ≥ 40 U/L (9, 10). Furthermore, pleural effusion due to rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and IgG4-related disease (IgG4-RD) can also show lymphocytic dominance and high concentrations of ADA (19, 20); therefore, autoimmune diseases with pleural effusion, such as RA, SLE, SjS, IgG4-RD, are difficult to distinguish from tuberculous pleurisy, even if thoracentesis shows a high ADA level.

A review of the literature revealed the characteristics of SjS with pleural effusion. Nine patients had high concentrations of anti-SS-A and/or anti-SS-B in their pleural effusion, findings that were similar to the serum data. Many patients were positive for serum ANA, and five were positive for ANA in both the serum and pleural effusion. With regard to the laterality of pleural effusion, 7 patients had bilateral effusion (53.8%), while 6 had unilateral effusion (46.2%). A previous review reported that pleural involvement in SjS was more often bilateral than unilateral (2). A pleural biopsy was reported in five case studies, with nonspecific findings noted. The biopsy was used to rule out tuberculous pleurisy and malignancies. Many patients were treated with steroid therapy, three received pulse corticosteroid therapy, and one received intravenous cyclophosphamide. Conversely, one patient was reported to experience natural remission. Another characteristic of SjS with pleural effusion is that the levels of complement components, such as C3 and C4, and the total complement levels in the pleural effusion are low, although the serum complement component levels are in the normal ranges (4, 9, 18), similar to the findings in our patient. The presence of anti-SS-A and/or anti-SS-B is thought to lead to pleuritis (5, 12); high concentrations of anti-SS-A and/or anti-SS-B in the pleural effusion may therefore be important for the diagnosis of SjS. There are no data on anti-SS-A and/or anti-SS-B in the pleural effusion in patients with other autoimmune diseases.

SjS with pleural effusion is very rare, and the possibility of secondary SjS should be considered (4). Secondary SjS is often associated with other autoimmune disorders, such as RA, SLE, and systemic sclerosis (1). In particular, the histological features of pleural disease in patients with SLE are lymphocytic and plasma cell infiltration and pleural fibrosis (2), with reduced levels of complement components (2), as in patients with SjS with pleural effusion (9, 18). Conversely, SjS patients usually have serum complement component levels within the normal ranges (5, 11-14), while SLE patients have reduced levels (2). In RA patients, thoracentesis shows low glucose levels in the pleural effusion (2), which is useful for distinguishing RA from SjS. Our patient was diagnosed with primary SjS because she had serum complement component levels within the normal ranges and normal glucose levels in the pleural effusion; she did not meet the diagnostic criteria for SLE (21) or RA (22). However, the characteristics of pleural effusion in secondary SjS have rarely been reported, so whether or not pleural effusion

Table. Literature Review of Cases of Sjögren's Syndrome with Pleural Effusion.

Case No.	Refer-ence	Age, Sex	Symptoms	Anti SS-A		Anti SS-B		ANA		PE			Pleural biopsy specimen	Treatment	
				Serum (U/mL)	PE (U/mL)	Serum (U/mL)	PE (U/mL)	Serum	PE	Predominant cells	LDH (U/L)	TP (g/dL)			ADA (U/L)
1	(15)	61, M	Cough, dyspnea	96.5	+	122	+	320x	ND	Right	Lymphocytes	ND	ND	ND	Prednisolone 40 mg
2	(11)	42, F	Chest tightness	320x	+	320x	ND	100x	100x	Bilateral	Lymphocytes	145	ND	12.0	Hydroxychloroquine 100 mg
3	(12)	58, F	Dyspnea	+	ND	-	ND	1280	ND	Bilateral	ND	ND	3.5	Normal	Methylprednisolone 500 mg
4	(14)	63, M	Cough, dyspnea, chest pain	256x	256x	-	ND	320x	320x	Bilateral	Lymphocytes	315	5.6	ND	Prednisolone 40 mg
5	(16)	65, M	Cough, dyspnea	>500	89.9	49	34.3	320x	80x	Left	Lymphocytes	ND	ND	ND	Methylprednisolone 500 mg
6	(17)	73, M	Dyspnea, edema	25.9	22.3	59.1	76.4	320x	ND	Bilateral	Lymphocytes	284	3.7	ND	Prednisolone 30 mg
7	(9)	45, F	Fever, skin rash	16x	16x	8x	4x	320x	320x	Bilateral	Lymphocytes	401	3.5	48.5	Prednisolone 40 mg
8	(18)	70, M	Cough, dyspnea	158.0	193.6	<10.0	-	1,280x	ND	Left	Lymphocytes	ND	5.6	ND	Prednisolone 30 mg
9	(13)	53, F	Cough, periorbital edema	+	ND	+	ND	160x	ND	Left	ND	ND	3.1	ND	Methylprednisolone 1,000 mg + cyclophosphamide 750 mg
10	(10)	40, F	Fever, right cervical pain	64x	ND	8x	ND	80x	ND	Bilateral	Lymphocytes	1,414	2.6	43	Prednisolone 60 mg
11	(5)	62, M	Chills, paleness of the fingers	16x	4x	8x	4x	320x	ND	Right	Lymphocytes	532	4.6	ND	Prednisolone 40 mg
12	(8)	64, F	Chest pain, cough	-	ND	+	ND	+	ND	Bilateral	Lymphocytes	ND	ND	ND	Natural remission
13	Present case	84, F	Dyspnea	>1,200	>1,200	563.0	656.0	160x	160x	Right	Lymphocytes	230	5.88	45.1	Prednisolone 20 mg

M: male, F: female, ANA: antinuclear antibody, SS-A: Sjögren's syndrome-related antigen A, SS-B: Sjögren's syndrome-related antigen B, ADA: adenosine deaminase, PE: pleural effusion, TP: total protein, LDH: lactate dehydrogenase, ND: not described

in patients with secondary SjS is similar to that in patients with SLE or RA is unclear.

Conclusion

We encountered a rare case of SjS with pleural effusion, high ADA levels, and positivity for anti-SS-A/anti-SS-B antibodies. It is important to distinguish patients with SjS with pleural effusion from those with tuberculosis pleurisy.

The authors state that they have no Conflict of Interest (COI).

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