Case Report Primary Sjögren's syndrome accompanied by pleural effusion: a case report and literature review

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Abstract: Sjögren's syndrome (SS) is a systemic autoimmune disease characterized by the infiltration of lymphocytes in exocrine glands, specifically the salivary and lacrimal glands, resulting in the typical symptoms of xerophthalmia and xerostomia. SS may be accompanied by pleural effusion when the lung is involved, but this occurrence has been reported in only 10 cases in the literature. We report the case of a 42 year-old woman with severe bilateral pleural effusion for eight years. Primary Sjögren's Syndrome was finally diagnosed based on the presence of xerophthalmia and xerostomia, biopsy of the minor salivary glands, and positive anti-SS-A antibody in the serum and pleural effusion. Biopsy of the parietal pleura through video-assisted thoracoscopy revealed infiltration of lymphocytes. The patient had a long history of pleural effusion without clear etiology. Malignant disease was first suspected because of abnormal density lesion on the left lung and malignant cells found on cytology, but PET-CT revealed no malignant lesion. Examinations did not support infection, malignant tumor, pulmonary sarcoidosis, or other connective tissue diseases. This data could be useful for the future study of pleural effusion in SS.

Keywords: Primary Sjögren's syndrome, pleural effusion, anti-SSA antibody

Introduction

Sjögren's syndrome (SS) is a systemic autoimmune disease characterized by the infiltration of lymphocytes in exocrine glands, especially the salivary and lacrimal glands, resulting in the typical symptoms of xerophthalmia and xerostomia [1-3]. Cases of SS involving the nose, pharynx, larynx, and vagina have been reported. The inflammation process usually severely damages and even destroys the glands [1-3]. SS may occur as a primary disease, or be secondary to another autoimmune connective tissue disorder [1-3]. Women are mostly affected (female to male ratio of 9:1) and the usual onset is in the middle age (40-50 years old) [1]. There is no known cure for SS. and treatment usually aims to symptom relief and prevention of complications including opportunistic infections due to the absence of saliva and tears, increased risk of hematological malignancy, depression, anxiety, sleep disturbances, and inflammation-associated disorders of the lungs, pericardia, liver, kidneys, nerves, and central nervous system [1-3].

Complications of lung involvement usually include chronic obstructive pulmonary disease (in 10%), bronchiectasis (in 8%), and interstitial lung disease (in 5%) [1-3]. The incidence of pleural effusion is extremely rare, occurring in less than 1% of patients with SS and mostly observed in Europe and Japan [4-7]. However, a Chinese study reported an incidence of pleural effusion of 5.7% in patients with SS, but did not mention if the pleural effusion was actually caused by SS [8].

The present paper reports the case of a 42 year-old woman with bilateral pleural effusion for eight years. This case provides more understanding about SS complicated by pleural effusion.

Case report

A 42 year-old female was admitted to Qilu Hospital (Jinan, Shandong, China) in March



Figure 1. Chest X-ray showing bilateral pleural effusion in a patient with SS.

2011 because of a history of intermittent chest tightness for eight years. Chest computed tomography (CT) showed bilateral pleural effusion. The discomfort disappeared after thoracentesis. The patient suffered from repeated recurrences. Three months before SS diagnosis, she consulted in our hospital for increasing chest tightness. Chest CT showed a large amount of bilateral pleural effusion and a highdensity lesion on the left lung (Figures 1 and 2). Brush cytology via fibro-bronchoscopy was suspect for heterocyst or malignant cells but positron emission tomography (PET)-CT revealed no malignant lesions, which was then suspect for compressed lung tissues. Symptoms were relieved after pleural effusion drainage, antiinfection drugs, intrapleural administration of interleukin (IL)-2, and dexamethasone (3 mg qd for 10 days). Ten days before diagnosis, chest tightness recurred. She was also suffering from xerophthalmia and xerostomia starting two years after the first episode of pleural effusion, and she gradually had lost 17 teeth over the years.

Physical examination revealed normal vital signs. Breath sound was coarse in bilateral upper lungs, and weak in lower lungs. Blood routine tests, urine routine tests, liver function, renal function, and tumor markers were all normal. The serum angiotensin-converting enzyme (SACE) was negative. Anti-tuberculosis antibody was weakly positive. Serological tests were positive for anti-SS-A antibody 1:320, anti-SSB antibody 1:320, and ANA 1:100. Rheumatoid factor (RF) levels were 61.60 IU/ml. Anti-neutrophil cytoplasmic antibodies (AN-CA) were normal. Anti-cyclic citrullinated peptide antibody (CCP) glucose-6-phosphateisomerand ase (GPI) levels were 0.14 mg/L (normal <0.2 mg/L) and 7.67 RU/ ml (normal <25 RU/ml), respectively. Serologic humoral immunity showed normal IgG (14.80 g/L), IgA (3.23 g/L), IgM (1.92 g/L), C₃ (1.07 g/L), and C_4 (0.181 g/L). Erythrocyte sedimentation rate (ESR) was 40 mm/h. Purified protein derivative of tuberculin (PPD) skin test was negative. X-ray of both hands showed no destructive

change. Chest X-ray and CT revealed bilateral pleural effusion.

The pleural effusion was exudative, with white blood cell count of 500×10^6 /L, including 98% of mononuclear cells. Lactate dehydrogenase levels were 145 U/L and adenosine deaminase levels were 12 U/L. Tuberculosis DNA test was negative. Multiple serum tumor markers were negative. Malignant cells were not found in the pleural effusion. Anti-SS-A antibody was positive, ANA 1:100 was positive, and RF levels were 75.30 IU/ml.

Multiple white nodules were observed on both parietal and visceral pleura by video-assisted thoracoscopy (**Figure 3**). Histopathological examination of a nodule on the parietal pleura revealed chronic inflammation of the pleura, pleural thickening and infiltrating of lymphocytes (**Figure 4**). Immunohistochemistry results of the specimen were positive for CD20 and CD3, and negative for LCA, CK, WT-1, TTF-1, CD99, CGA, and Syn.



Figure 2. Chest CT showing bilateral pleural effusion and abnormal density lesion in the left lung.

Patient's eyes were dry with an abnormal Schirmer's test (right eye 5 mm, left eye 4.5 mm). Most teeth were decayed and 17 have been lost. Her mouth was dry with reduced secretion of saliva. Biopsy of the little salivary glands in the lower lip revealed infiltration of lymphocytes (**Figure 5**).

She was then diagnosed with SS. She then received hydroxychloroquine (100 mg bid) and total glucosides of paeony (TGP, a capsule of extracts of traditional Chinese medicine). After 1 month, pleural effusion was greatly reduced, but has not completely disappeared. She has been followed up for 4 years, without recurrence of the pleural effusion.

Discussion and review of the literature

The case reported here was diagnosed with SS according to the American and European Consensus Group classification criteria (AECG-criteria) [9]. First, the patient had been suffering from xerophthalmia and xerostomia for several years. Biopsy of the little salivary glands

revealed diffused infiltration of lymphocytes. In addition, anti-SSA antibody in both serum and pleural effusion was positive. There was no evidence supporting other connective tissue diseases.

In the case reported here, differential diagnoses of infection or malignant disease for the pleural effusion were unlikely. Indeed, blood routine tests and temperature were normal. Pleural effusion was not neutrophilic, ruling out bacterial infection. Tuberculous pleuritis may be lymphocytic, but in this case, TB DNA and PPD skin tests were negative. Furthermore, adenosine deaminase (ADA) was rather low. Although a suspect mass was found on the left lung by CT and malignant cells were found on bronchus cytology, no malignant cells were found in the effusion, and tumor markers in serum and pleural effusion were normal. In addition, PET-CT revealed no hypermetabolic lesion. Biopsy of the parietal pleura revealed chronic inflammation of the pleura and infiltration of lymphocytes. Immunohistochemistry demonstrated CD20 and CD3 positivity. There-

Sjögren's and pleural effusions



Figure 3. Video-assisted thoracoscopy showing showed adhesive bands and white nodules on the pleura.



Figure 4. Histology of a nodule taken from the parietal pleura showing chronic inflammation of the pleura, pleural thickening, and infiltration of lymphocytes.

fore, in the absence of further proof, the suspect lesion of the left lung might be compressed lung tissues. Pulmonary sarcoidosis was ruled out by negative SACE results and pleural biopsy [10]. RF levels in serum and pleural effusion were 61.60 IU/ml and 75.30 IU/ml, respectively. Pleuritis is more often caused by



Figure 5. Histology of the little salivary glands in the lower lip revealing infiltration of lymphocytes in the glands.

rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) than other connective tissue diseases [4]. However, in this case, pleural effusion was not induced by RA because the patient did not complain of morning stiffness, arthralgia, or deformation of any joints, and because levels of serum anti-CCP antibody and GPI were both negative. X-ray of both hands was normal. Therefore, the possibility of SLE was even smaller. Although ANA 1:100 was positive, the typical characteristics such as discoid rash, malar rash, photosensitivity, arthritis, renal lesion, and anti-ds-DNA antibody or anti-Sm antibody were lacking.

Few cases of primary SS with pleural effusion have been reported. Indeed, only 13 cases of primary SS with pleural effusion have been described so far [5-7, 11-19]. However, a Chinese study in 573 patients with primary SS reported an incidence of pleural effusion of 5.7% [8], but they did not describe these cases nor provided any details. This higher incidence might be due to the population being studied or

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to the diagnostic methods. Teshigawara et al. [7] reported a 65-year-old patient diagnosed with primary SS with bilateral pleuritis and large pleural effusions based on xerophthalmia, xerostomia, positive results for anti-SS (anti-SS-A/SS-B) antibodies, Schirmer's test, and biopsy of the minor salivary glands. Ogihara et al. [6] described a 62-year-old man with subclinical SS as he only met the laboratory (increased SS-A/SS-B antibodies) and histological criteria without complain of xerostomia; there was no other disease that could explain the pleural effusion. Kawamata et al. [5] reported a patient with primary SS who presented with pleural effusions as the initial manifestation of the disease, as was the case in the patient reported here. Horita et al. [15] reported the case of a 73-year-old man with concomitant pleural effusion and nephrotic syndrome; he was later diagnosed with SS based on immunology and immunohistochemistry, while the nephrotic syndrome was caused by type II diabetes. Makimoto et al. [17] reported a case in which bilateral pleural effusion was the only symptom at presentation. Ohe et al. [18] reported a case of SS presenting with pleural effusion, pericardial effusion, and ascites. Yamasaki et al. [19] reported a case of SS with pleural effusion that could have been due to pulmonary vein hypertension.

Increased levels of ANA in the pleural effusion were reported in three cases [7, 13, 14], as in the present case. Positive anti-SS-A and anti-SS-B have been reported in five cases [5-7, 14, 15], as observed in the present case, but have also been reported to be negative in the pleural effusion [16]. All reported cases had lymphocyte infiltration [5-7, 11, 12, 14-19]. A review of nine cases reported that elevated levels of SS-A/SS-B antibodies, lymphocytosis, and low levels of complement in the pleural fluid were common features of SS-associated pleural effusion [20].

The present case was the first to use thoracoscopy to explore the pleural cavity in search for lesions. It was particularly helpful for detecting and analyzing pleural lesions, and to help determining the inflammatory and autoimmune nature of the disease.

The exact cause of pleural effusion in patients with SS is unknown. It is assumed that cytokines from CD4+ T lymphocytes may activate B lymphocytes. Then, the activated B lymphocytes produce autoantibodies that are associated with pleuritis and other systemic tissue damage [6]. Kawamata et al. [5] reported T cell receptor beta-chain variable region gene bias and local autoantibody production in the pleural effusion; they suggested that a common biased T cell response might play a critical role in this manifestation. Further study is necessary to understand the occurrence of pleural effusion in SS.

Although the rarity of SS-associated pleural effusion precludes any firm conclusion about treatments, it seems that controlling the systemic inflammation yield good results, as in classical primary SS [21]. Indeed, Tanaka et al. [14] and Makimoto et al. [17] treated their patient with corticosteroids, with good effects. Ohe et al. [18] successfully treated their case with high-dose corticosteroids. Kashiwabara et al. [12] treated their patient with prednisolone and all symptoms disappeared within a month.

In conclusion, despite the fact that pleural effusion is a rare manifestation of SS, a diagnosis of SS might be considered in patients presenting with pleural effusion in the absence of any clear etiology. However, these patients require a close follow-up and further testing to make the correct definitive diagnosis.

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Disclosure of conflict of interest

None.

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