A Case of Sjogren's Syndrome Accompanied by Signs of Non-Cardiac Pulmonary Edema and Infection

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ABSTRACT

At first presentation connective tissue diseases may mimic infectious diseases. But recurrent non-cadiac pulmonary edema accompanied by serious infectious signs is observed rarely. This patient presented with signs of pneumonia, and developed recurrent non-cadiac pulmonary edema, and had to be intubated despite appropriate treatment and Sjögren's syndrome was diagnosed after examinations and detailed history which were warranted by lack of treatment response. She was treated with hydroxychloroquine. This patient's problem was thought to be due to both findings of systemic involvement of connective tissue disease and increased frequency of infectious diseases in these patients. Key Words: Sjögren's syndrome, non-cadiac pulmonary edema, infection

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NON-KARDİYAK AKCİĞER ÖDEMİ VE ENFEKSİYON BULGULARININ EŞLİK ETTİĞİ SJÖGREN SENDROMU OLGUSU

ÖZET

Konnektif doku hastalıkları ilk başvuru sırasında enfeksiyon hastalıklarını taklit edebilir. Fakat böyle bir hastada ciddi enfeksiyon bulgularının eşlik ettiği tekrarlayan non-kardiak akciğer ödemi nadir görülen bir durumdur. Pnömoni bulguları ile başvuran, uygun tedaviye rağmen tekrarlayan non-kardiyak akciğer ödemine giren ve entübe edilen hastanın takibinde tedavi yanıtsızlığı nedeniyle yapılan araştırmalar ve öyküsünün derinleştirilmesi sonucu Sjögren sendromu tanısı konuldu. Hidroksiklorokin ile tedavi edildi. Hastada görülen bu durumdan hem konnektif doku hastalığının sistemik tutulum bulgularının hem de bu hastalarda görülebilen enfeksiyonlara yatkınlığın artmış olmasının sorumlu olabileceği düşünüldü.

Anahtar Kelimeler: Sjögren sendromu, non-kardiyak akciğer ödemi, enfeksiyon **Nobel Med 2013; 9(2): 126-129**

INTRODUCTION

Sjögren's syndrome (SS), is a systemic autoimmune disease characterized basically by lymphocytic infiltration of exocrine glands. Its course is marked by dry eyes and mouth due to dysfunction of lacrimal and salivary glands. It is called as primary SS if no association with another autoimmune disease could be established.[1,2]

SS is not only a syndrome of dryness but it also causes extra glandular and systemic involvement. Extra glandular involvement may sometimes be serious and life threatening. Joint involvement, Raynaud phenomenon, central and peripheral nervous system involvement, and systemic findings such as renal and pulmonary involvement are seen in two thirds of these patients.[1,2]

The patients with SS may sometimes present with signs that mimic signs of several infectious diseases. This may be due to both the systemic involvement of an undiagnosed connective tissue disease and the increased vulnerability to infectious diseases because of the disease[3].

CASE

A 69 years old woman was admitted to our clinic with chills, cough, dyspnea and left pleuritic chest pain. She described cough for three weeks and fever, dyspnea and chest pain for a week. Rare rales at left basal lung were detected by physical examination and a mild infiltration at left lung was detected by chest X-ray led to diagnosis of pneumonia. Cefuroxime axetil was started. Patient didn't recover during outpatient follow up, her fever reached 39ºC and she was hospitalized. Her family history did not reveal any information. She had hypertension (for 30 years) and 1-2° mitral insufficiency. At physical examination vital signs were stable but rare rales at left lung base persisted. Hematologic workup at admission revealed the following data: hemoglobin level: 11.4 gr/dl (11-16.5 gr/dl), leukocyte count: 14,200/mm^3 (4,000-10,000/mm^3), thrombocyte count: 672,000/mm^3 (150,000-400,000/mm^3), erythrocyte sedimentation rate: 70 mm/h (0-20 mm/h), CRP: 155 mg/L (0-5 mg/L). Other laboratory results were within normal limits. Chest X-ray was normal except blunted sinuses. Ceftriaxone 2 g/day was started. At first day of admission, she developed a sudden dyspnea. Blood pressure was normal, and apical cardiac beat was at sinus rhythm.

Hypoxia and mild respiratory acidosis were detected. She was intubated and mechanically ventilated. Laboratory tests at this time were as follows: leukocyte count: 29,900/mm^3, thrombocyte count: 864,000/mm^3, CRP: 168 mg/L. She had no fever and there wasn't any pathological sign except pulmonary findings. Echocardiography showed normal cardiac function. Chest tomography revealed linear atelectasis at both lower lobes, bilateral mild pleural effusion, and minimal pericardiac effusion. At second day of admission, pulmonary functions rapidly improved and she was extubated. Blood gas values were regulated only by mechanical ventilation without any need for corticosteroid treatment. At fifth day, she was generally in a better condition but there wasn't a significant clinical improvement. Leukocyte count was 19,400/mm^3, and CRP was 174 mg/L so antibiotic treatment was changed to cefoperazone/ sulbactam 4 g/day. No growth was detected in cultures which were taken at admission. Results of viral markers and Gruber Widal test were negative. At fifth day of cefoperazone/ sulbactam dosing, hematologic markers continued to get worse: leukocyte count was 26,900/mm^3, and CRP was 234 mg/L. Pulmonary findings did not resolve completely and treatment was changed to imipenem 4x500 mg and linezolid 2x600 mg. Blood values started to improve at fifth day with the new antibiotic treatment (leukocyte count: 9200/mm^3, thrombocyte count 829,000/mm^3, CRP: 38 mg/L). At seventh day of imipenem and linezolid treatment pulmonary edema developed for the second time with a sudden onset of dyspnea. The patient was intubated again and mechanically ventilated. Her blood values were also worsened again (leukocyte count: 21,300/mm^3, thrombocyte count: 1,066,000/mm^3, sedimentation rate: 105 mm/h, CRP: 256 mg/L). Clarithromycine was added to her treatment. Repeated echocardiography showed minimal pericardial effusion. This condition was thought not cardiac origin. Pulmonary functions improved rapidly the day after and she was extubated. Corticosteroid was not administered neither of the non-cardiac pulmonary edema attacks. Respiratory acidosis was at a mild level and blood gas values improved rapidly. Fever was not detected at her follow up and immunologic investigations were started. Tumor markers and immunoglobulin levels were normal. Ferritin and transferrin levels were normal and we could not detect any atypical cells in peripheral blood smear. Bone marrow aspiration biopsy was made and massive increase was detected in plasma cells. She was assessed for multiple myeloma. No additional finding could be detected and follow up was advised. She did not have fever at any time starting from her admission and no growth was detected at repeated cultures and cultures of pleural fluid samples. When patient's history, clinical and laboratory findings were evaluated, polymyalgia rheumatica and adult onset Still's disease were not considered. Screening results for autoimmune diseases were as follows: Anti-nuclear antibody (ANA) 1/320 granular pattern, anti-Ro (SS-A) and rheumatoid factor (RF) were positive. Anti-La (SS-B) and anti-double →

Table 1: Revised international classification criteria for Sjogren's syndrome

I. Ocular symptoms: 1. Daily, persistent, troublesome dry eyes for more than 3 months 2. Recurrent sensation of sand or gravel in the eyes 3. Use tear substitutes more than 3 times a day
II. Oral symptoms: 1. Daily feeling of dry mouth for more than 3 months 2. Recurrently or persistently swollen salivary glands as an adult 3. Frequently drink liquids to aid in swallowing dry food
III. Ocular signs 1. Schirmer's test 2. Rose bengal
IV. Histopathology In minor salivary glands focal lymphocytic sialoadenitis, evaluated by an expert histopathologist, with a focus score >1, defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm^2 of glandular tissue
V. Salivary gland involvement: 1. Unstimulated whole salivary flow 2. Parotid sialography 3. Salivary scintigraphy
VI. Autoantibodies: Antibodies to Ro(SSA) or La(SSB) antigens, or both

Primary SS	Secondary SS
a. The presence of any 4 of the 6 items is indicative of primary SS, as long as either item IV or VI is N positive b. The presence of any 3 of the 4 objective criteria items (that is, items III, IV, V, VI) c. The classification tree procedure represents a valid alternative method for classification, although it should be more properly used in clinical-epidemiological survey	In patients with a potentially associated disease (for instance, another well defined connective tissue disease), the presence of item I or item II plus any 2 from among items III, IV, and V may be considered as indicative of secondary SS

Exclusion criteria: Past head and neck radiation treatment Hepatitis C infection Acquired immunodeficiency disease (AIDS) Pre-existing lymphoma Sarcoidosis Graft versus host disease Use of anticholinergic drugs

stranded DNA (anti-dsDNA) were negative. Dry eye of the patient was confirmed with Schirmer's tear test getting wet 3 mm per 5 minutes. A biopsy of the salivary gland revealed grade 4 chronic lymphocytic sialadenitis based on Chilsom classification. The presence of RF, ANA, and anti-Ro (SS-A) autoantibodies, grade 4 chronic lymphocytic sialadenitis on biopsy of the salivary gland along with the clinical findings revealed Sjogren's syndrome. The patient was treated orally with hydroxychloroquine (400 mg/day) and artificial tears.

DISCUSSION

Frequency of SS was reported to be 0.6-0.1%.[2,4,5] According to our observation a patient present with serious infectious signs and recurrent pulmonary edema was rarely diagnosed as SS.

SS is a connective tissue disease characterized by Sicca syndrome which is defined by insidious onset of eye and mouth dryness.[2,3,6] Diagnosis is usually made 10 years after disease onset and generally after several medical consultations.[3,7] SS is typically seen in women (F/M=9/1) and it starts between 4-6. Decades.[3,8-11] SS may co-exist with other autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematous (SLE), and progressive systemic sclerosis.[11] In addition, patients should be assessed at diagnosis in terms of other autoimmune conditions. Patient's age, clinical findings and laboratory results are important in this assessment. Since our patient had evidently high leukocytosis and CRP, Yamaguchi criteria for adult onset Still's disease were evaluated.[12] Adult onset Still's disease was ruled out due to positive ANA results, normal ferritin level, and absence of findings like arthritis, arthralgia, and typical rash. Moreover, polymyalgia rheumatica, which is an inflammatory rheumatologic disease with morning stiffness in shoulders and hip in the elderly, was evaluated in differential diagnosis.[13] However, it was ruled out due to the absence of morning stiffness in our patient's shoulders and hip. Although SS is not typically seen in cases with similar age and the sex with this presented case the mouth and eye dryness in detailed anamnesis were consistent with SS symptoms. No accompanying autoimmune disease could be defined.

Initial SS symptoms may mimic bacterial pneumonia and tuberculosis.[3] Further infections, particularly pneumonia and upper and lower respiratory tract infections are seen more frequently in these patients due to increased vulnerability to bacterial infections.[14] Recurrent respiratory tract infections are reported in 10-35% of patients. For this reason diagnosis may be difficult at first presentation.[2] Pulmonary involvement as a systemic finding in patients with primary SS is reported to be 9-12 %.[1,4,15] Tracheobronchial dryness and impaired mucociliary cleaning are among factors of increasing vulnerability to pulmonary infections.[14] Sicca cough and mild-moderate airway obstruction may be observed due to pulmonary involvement. Interstitial pneumonia and bronchiolitis due to pulmonary involvement are the most commonly observed pathologies. However, interstitial lung disease and pleural involvement are rarely presenting signs.[2,16] Significant signs may be lacking in chest X-ray and chest tomography of these patients. Hypergammaglobulinemia and anti-Ro (SS-A) positivity are more commonly observed in cases with pulmonary involvement.[2] Tomography of the patient showed linear atelectasis at both lower lobes, bilateral mild pleural effusion, and minimal pericardiac effusion. The initial examination results of the patient were consistent with pneumonia; therefore, antibiotic treatment was initiated primarily. However, after this administration the patient →

developed non-cardiac pulmonary edema following acute dyspnea twice and rapidly recovered by only mechanical ventilator support; thus, pulmonary embolism and other pulmonary pathologies were re-assessed. Pulmonary embolism is an emergency condition with high mortality if it is not diagnosed and treated timely. In the presence of acute dyspnea, it should be evaluated in differential diagnosis.[17] Pulmonary embolism was not detected in the ventilation perfusion scintigraphy of the patient whose D-dimer level was normal during the tests performed for diagnosis of pulmonary embolism. The patient's non-cardiac pulmonary edema attacks were treated by mechanical ventilation and blood gas values returned to normal. Since both SS and infection were responsible for the clinical picture, full recovery could not be achieved before diagnosis had established.

Serologic studies in SS should include assessment of RF and ANA. Although these markers are not specific for SS they are important markers of autoimmunity. Anti-Ro (SS-A) and anti-La (SS-B), are more specific markers for SS but they may be positive in many other conditions including SLE. Serologic markers such as ANA, RF, anti-Ro (SS-A) and anti-La (SS-B) may be positive in SS.[9] In a study of 400 SS patients clinical picture of primary SS was similar in young and elderly patients but immunologic properties were less common in the elderly.[1] Clinical findings and immune system response of elderly patients may not be complete. Therefore, elderly patients may manifest atypical findings. Our patient also had an atypical clinical course. ANA and anti-Ro (SS-A) antibodies were positive in our patient.

American-European consensus criteria which were revised in 2002 are used for diagnosis of SS (Table 1).[18] Schirmer's tear test was used for the evaluation of tear secretion by the lacrimal glands. There was wetting of less than 5 mm per 5 minutes. It demonstrated strong indication of diminished secretion. Eye dryness of the patient was confirmed with Schirmer's tear test getting wet 3 mm per 5 minutes. A biopsy of the salivary gland revealed grade 4 chronic lymphocytic sialadenitis based on Chilsom classification.[19] According to these criteria primary SS diagnosis was made with mouth-eye dryness for more than 3 months, positive Schirmer test, Anti SS-A positivity, consistent salivary gland biopsy, and absence of another autoimmune disease.

CONCLUSION

At initial presentation, connective tissue diseases such as SS, may be overlooked in previously undiagnosed patients. However, vulnerability of these patients to infections should be kept in mind. Connective tissue diseases should be considered in patients who present with infectious findings and do not have good treatment response.

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