Fulminant Pneumonitis: A Clue to Autoimmune Disease

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We report a 65 year old woman who presented with a 2 week history of fever, dry cough and dyspnea, and developed severe interstitial lung disease. High titers of antinuclear antibodies, anti-SS-A, anti-SS-B, and hyperglobulinemia strongly support the fact that her fulminant pneumonitis was probably due to previously unrecognized Sjogren’s syndrome. Similar cases of severe interstitial lung disease as the first presentation of autoimmune conditions are discussed.

PATIENT DESCRIPTION

A 65 year old woman presented to our emergency department with a 2 week history of fever up to 39°C, dry cough and shortness of breath. Her medical history included hypertension, nephrolithiasis with right nephrectomy (performed 20 years ago) and asthma treated with a long-acting beta agonist/corticosteroid inhaler. The patient denied a history of rash, arthralgia, arthritis, aphthea or a family history of connective tissue disease. Clinical and chest radiographic findings were suggestive of right lower lobe pneumonia. Despite oral antibiotic therapy, her fever, dry cough and dyspnea persisted; she also developed leg edema and was admitted to hospital.

On admission her respiratory rate was 20 breaths per minute and oxygen saturation was 95% in room air. Fine crackles were heard over the lower third of the right lung, without reduced air entry or dullness on percussion. Pitting edema of both lower extremities was present. Otherwise, the physical examination was unrevealing. Her blood tests showed mild anemia (hemoglobin 11 g/L, mean cell volume 78 fl), normal number of white blood cells and platelets, normal level of serum electrolytes, urea and creatinine; reduced albumin (2 g/dl, normal > 3.5 g/dl) and elevated lactate dehydrogenase (365 U/L, normal < 225). Erythrocyte sedimentation rate was 40 mm/hr (normal < 20 mm/hr) and C-reactive protein was 65 U/L (normal < 5 U/L).

Chest radiographic findings were similar to those of the previous examination. Blood and sputum cultures were sterile. Tests for Q fever, Mycoplasma, Rickettsia, Chlamydia pneumonieae, Legionella, hepatitis B virus, hepatitis C virus, human immunodeficiency virus, Epstein-Barr virus, cytomegalovirus and parvovirus were negative. Antibiotic therapy was changed to levofloxacin with no amelioration of dyspnea and fever. She developed an erythematous maculopapular rash on the right calf. Chest computed tomography disclosed ground-glass opacities, multiple peripheral nodular interstitial infiltrates and small pleural effusions [Figure].

Considering the progressive respiratory failure and radiologic deterioration despite wide-spectrum antibiotic treatment, the diagnosis of bronchiolitis obliterans with organizing pneumonia was suspected. Prednisone 40 mg/day was started, followed by disappearance of the rash but appearance of arthritis in the knees, elbows and ankles. Fundus examination of her eyes demonstrated large amounts of cotton-wool spots and small amounts of retinal hemorrhage. A repeat medical history revealed severe fatigue, weakness and a feeling of dry mouth and eyes for several months prior to her current illness. Blood tests were taken for connective tissue diseases, including anti-CCP, antinuclear antibody, anti-neutrophil cytoplasmic antibody, anti-SS-A,

Chest CT at the level of inferior pulmonary veins lung manifests as reticular interstitial shadows in the lower lobe more prominent on the right and at the periphery of the right middle lobe. A small amount of bilateral pleural effusion is also seen.
The patient presented with fulminant pneumonitis in the context of a systemic illness with fever, weight loss, protracted myalgia, fatigue and muscle weakness, rash, arthritis, and signs of vasculitis on fundus examination. Her lung disease responded neither to various antibiotic regimens nor to glucocorticoids. She had long-lasting unrecognized mouth and eye dryness. During her short period of hospitalization, the working diagnosis was connective tissue disease with signs of systemic vasculitis. Positive tests for ANA, anti-SS-A and anti-SS-B antibodies and hyperglobulinemia obtained after her death supported the diagnosis of primary Sjogren's syndrome, first manifested by systemic illness and fulminant interstitial lung disease. Our patient fulfilled only some of the criteria of pSS: antibodies to anti-SS-A and anti-SS-B, and eye and mouth dryness. Her severe condition did not allow performance of Schirmer’s test, Rose Bengal staining, or salivary gland biopsy. Hyperglobulinemia and her past history of nephrolithiasis could indirectly support the diagnosis of pSS.

Lymphocytic infiltration and destruction of the exocrine glands, xerostomia and xerophthalmia are hallmarks of pSS. Involvement of the respiratory tract has been reported in pSS [1]. It may be presumed that the patient’s “asthma” could be due to xerotrachea. Lung involvement in primary Sjogren’s syndrome mainly presents as lymphocytic interstitial pneumonia. Other forms of pSS-related lung changes have been described: non-specific interstitial pneumonia, usual interstitial pneumonia, bronchiolitis obliterans with organizing pneumonia, lymphoma, and pulmonary arterial hypertension. The frequency of pulmonary involvement in primary Sjogren’s syndrome varies from 9% to 75%. Pulmonary complications occur early in the course of the disease and predominantly in patients positive for anti-SS-A antibodies [2]. The majority of patients with ILD and pSS were female (more than 80%), with age at ILD onset ranging from 34 to 78 years. In the Parambil series [1], of 18 patients with pSS and ILD, 4 (22%) had both pSS and ILD diagnosed within one month of their initial presentation. The presenting symptoms of interstitial lung disease associated with primary Sjogren’s syndrome include dyspnea, dry cough, chest pain, wheeze, fever, digital clubbing and sicca symptoms. Inspiratory crackles and expiratory wheezes are the most common findings on physical examination.

All patients without exception had high titers of positive ANA, anti-SS-A and/or anti-SS-B antibodies. Elevated erythrocyte sedimentation rate, significant hyperglobulinemia and high titers of rheumatoid factor were frequent (in our institute, only the anti-CCP test is available and it was negative). Chest X-rays often demonstrated bilateral lung infiltrates and fibrosis. High resolution chest computed tomography showed bilateral ground-glass, consolidative, reticulonodular opacities, cysts, traction bronchiectasis, honeycombing, large nodules and masses, and prominent interlobular septal thickening [3]. The majority of pSS patients have a prominent restrictive pattern on pulmonary function tests; obstructive changes have also been reported [2].

Few cases with rapidly progressive interstitial lung disease associated with primary Sjogren’s syndrome have been described [Table]. Fulminant lung disease as the first clinically significant presentation of pSS is extremely rare. The treatment of rapidly progressive ILD related to connective tissue disease is a considerable challenge and has been better studied in dermatomyositis. Kameda et al. [4] compared two groups of patients with dermatomyositis and interstitial pneumonia who received either methylprednisolone alone or in combination with cyclophosphamide and cyclosporine, and showed that the combination group had a better

**COMMENT**

- **ANA** = antinuclear antibody
- **Ig** = immunoglobulin
- **ANCA** = anti-neutrophil cytoplasmic antibodies
- **pSS** = primary Sjogren’s syndrome
- **ILD** = interstitial lung disease

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anti-SS-B, anti-centromere, anti-SCL70, anti-RNP, anti-Sm, anti-dsDNA, anticardiolipin antibodies, complements C3 and C4, lupus anticoagulant, serum protein electrophoresis and immunoelectrophoresis. The results were pending. Urine test was normal. Echocardiography showed mild mitral regurgitation and mild pulmonary hypertension. Therapy with intravenous methylprednisolone 1 g/day for 3 days followed by oral prednisone 60 mg/day was started. Following pulse therapy, the patient reported amelioration of weakness, fever and arthritis, but the respiratory manifestations continued to deteriorate. A single pulse of cyclophosphamide 500 mg was given intravenously. The next day, the patient complained of new-onset chest pain with subsequent serum troponin elevation up to 4.2 ng/ml (normal < 0.2) without ECG changes suggestive of myocardial ischemia. Repeat echocardiography demonstrated inferior wall and septal hypokinesia along with moderate mitral regurgitation. Her oxygen saturation decreased to 90% and she was oxygen dependent. Rituximab, monoclonal anti-CD20 antibodies, was added intravenously in 1 g doses.

Two days later the patient developed multi-organ failure, including acute myocardial infarction, pancreatitis and cardiogenic shock. Fourteen days after admission, she died. The family refused a postmortem autopsy. Thereafter, the following laboratory tests were received: ANA 7.9 U/L (normal < 1.1 U/L), anti-SS-A strongly positive, anti-SS-B positive, immunoglobulin G 1780 mg/dl (normal 680–1560 mg/dl), IgA 416 mg/dl (normal 70–350 mg/dl), IgM 60 mg/dl (normal 40–280 mg/dl), anti-dsDNA negative, anti-Sm negative, anti-RNP negative, anti-SCL70 negative, and ANCA negative. A diagnosis of primary Sjogren’s syndrome associated with acute interstitial pneumonitis was strongly suggested.
Report on primary Sjogren’s syndrome presenting first with severe pulmonary involvement

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<tr>
<th>Ioannou S</th>
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<tr>
<td>Rheumatol Int</td>
<td>J Assoc Physicians India</td>
<td>Ann Med Interne (Paris)</td>
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<td>2008</td>
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- **Age (yr)**: 70, 52, 24–70
- **Gender**: Female, Female, 4 females, 1 male
- **General clinical manifestations**:
  - Fever, sicca syndrome
  - Fever, weakness, dental caries
  - Sicca syndrome (n=5), positive Schirmer test (n=5), arthralgia (n=4), myalgia (n=5), Raynaud’s phenomenon (n=2)
- **Respiratory features**:
  - Dry cough, dyspnea, lung crepitus
  - Dry cough, dyspnea, lung crepitus
  - Dyspnea (n=5), cyanosis (n=2), clubbing (n=5), lung crepitus (n=5), high neutrophil and eosinophil count on bronchial lavage (n=5), severe restrictive pattern with reduced diffuse capacity (n=4)
- **Duration of symptoms**: 2 months, 1 year, Unknown
- **Imaging**:
  - RLL infiltrate
  - Reticulonodular shadows in lower lobes, honeycombing and advanced interstitial fibrosis
  - Interstitial pneumonitis
- **Lung biopsy**:
  - Cryptogenic organizing pneumonia
  - Not performed
  - Severe fibrotic changes
- **Treatment**:
  - Steroids
  - Oxygen, steroids, bronchodilators
  - Steroids
- **Outcome**:
  - Improvement
  - Not reported
  - 2 patients died

short-term outcome; however, overall mortality was high and did not differ in both groups [4]. ILD associated with connective tissue disease usually has a more severe course than idiopathic ILD and generally is treated more aggressively. In the majority of reported cases and series, glucocorticoids remain the cornerstone of the majority of reported cases and series, generally is treated more aggressively. In severe course than idiopathic ILD and connective tissue disease usually has a more severe course than idiopathic ILD and generally is treated more aggressively. In the majority of reported cases and series, glucocorticoids remain the cornerstone of treatment [1]. Other immunosuppressive agents are usually used and include cyclophosphamide, azathioprine and cyclosporine, but their effect is questionable. In a few patients with severe ILD related to connective tissue disease resistant to high doses of corticosteroids and standard immunosuppression, rituximab contributed to stabilization of lung disease [5]. In conclusion, fulminant interstitial lung disease may be the presenting manifestation of a previously unrecognized primary Sjogren’s syndrome; as in our patient, it may have an uncontrolled and fatal course. Progressive respiratory failure associated with systemic signs and changes on chest CT findings unresponsive to broad-spectrum antibiotics may be a clue for the diagnosis of ILD due to unrecognized underlying connective tissue disease. Searching for specific autoantibodies (anti-SS-A and/or anti-SS-B), tests for eye dryness, or salivary gland biopsy will contribute to the diagnosis of underlying pSS in patients with unexplained fulminant ILD and systemic signs. The role of high doses of corticosteroids and early aggressive immunosuppressive therapy for rapidly progressive ILD in pSS has not been established and needs further evaluation.

### References


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“Ambition is like hunger; it obeys no law but its appetite”

Josh Billings (1818-1885), American columnist and humorist

“Only mediocrity can be trusted to be always at its best. Genius must always have lapses proportionate to its triumphs”

Max Beerbohm (1872-1956), British essayist, parodist, and caricaturist

“Love all, trust a few, do wrong to none”

William Shakespeare (1564-1616), English poet and playwright, considered the greatest writer in the English language and the world’s pre-eminent dramatist playwright and poet