CASE REPORT

Lymphocytic interstitial pneumonia as a manifestation of SLE and secondary Sjogren's syndrome

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SUMMARY

A 47-year-old woman with systemic lupus erythematosus (SLE) diagnosed at age of 35 years was admitted for dyspnoea, substernal chest pain, dry mucosae and difficulty in swallowing. Physical examination revealed vesicular breath sounds bilaterally. Laboratory work showed antinuclear antibody (ANA) (speckled pattern, 1:40), positive anti-Sjogren's syndrome antigen (SSA) and antisingle side band (SSB) and negative double-strand DNA (dsDNA), with normal C3, C4, C50. A high-resolution chest CT scan demonstrated multiple bronchial cysts and diffuse interstitial infiltrates. Surgical lung biopsy revealed emphysematous changes and mild lymphocytic infiltrate around the bronchioles compatible with lymphocytic interstitial pneumonia diagnosis. This case illustrates a patient with primary SLE overlapped by initial manifestations of secondary Sjogren's syndrome (SS) presenting with associated autoimmune interstitial lung disease. Antibody markers, high-resolution chest CT scan and surgical lung biopsy were essential in evaluating this patient, confirming the interstitial lymphocytic infiltration of the lung. Primary SS (pSS) is the most commonly associated disease to lung interstitial pneumonia (LIP) (25%). High-resolution chest CT scan demonstrates areas of ground-glass attenuation, suggestive of interstitial disease. Surgical lung biopsy shows pathologic increase of mature lymphocyte cells and histiocytes. Most of the cases have a benign presentation and shortly relapse. Superimposed infection, pulmonary fibrosis and lymphoma develop in less than 20% of cases. Corticosteroids are the primary therapy. While pSS is commonly associated with interstitial lung involvement, secondary Sjogren's syndrome (SSS) is only rare. It has been described the initial SSS presentation by Sica symptoms development only, and our case is the first report of LIP presentation as initial manifestation of SSS. Our patient remained stable after corticosteroids and hydroxychloroquine therapy and no progression of disease after 6 months follow-up.

BACKGROUND

Lung interstitial pneumonia (LIP) is an inflammatory pulmonary reaction to various stimuli, mainly systemic disease or infection. In the order of association, LIP occurs commonly in autoimmune diseases (25–39%) as Sjogren's syndrome (SS)¹ and SLE² followed by infectious causes (14%), mainly in persons who are seropositive for HIV and/or infected with Epstein-Barr virus.³ The incidence of LIP is greater in women than in men. The average age at diagnosis is between 40 and 60 years. It generally presents with progressive cough and

dyspnoea. Diagnosis requires lung biopsy or bronchoscopy with sampling.

SS is an autoimmune inflammatory disease characterised by the lymphocytic inflammation of exocrine glands. It leads to dryness of the mucosa of the mouth and eyes, leading to the sicca syndrome. In addition, other organs can be involved, including the joints, gastrointestinal tract, cardiovascular system and lungs.⁴ Although many cases of LIP are associated to autoimmune disease, secondary SS (sSS) very rarely manifests with LIP.⁵ We describe a case of a patient with SLE presenting with overlapping SS accompanied by LIP. There are some other common pulmonary presentations that are more frequently seen in systemic lupus erythematosus (SLE) and SS than in LIP. Therefore, this rare clinical presentation turned the case to be more challenging, requiring more investigative studies with lung biopsy; by doing bibliography review, we concluded that this case was worth being published.

CASE PRESENTATION

A 47-year-old African-American woman was admitted for worsening shortness of breath, and acute onset of retrosternal chest pain without radiation. The patient also reported recent onset of dry eyes, dry mouth and difficulty in swallowing. She also endorsed dry cough for the past couple of weeks, but denied sputum, fevers, chills or shivers. She also denied any sick contacts or recent travel or hospitalisation. Her medical history was remarkable for SLE diagnosed at the age of 35. At that time of diagnosis, she presented with symptoms of malar rash, photosensitivity, arthritis of the knees, antinuclear antibody (ANA) 1:160 and positive antibodies to double-stranded DNA (dsDNA). She had been taking prednisone and hydroxychloroquine and has never been admitted for SLE flare. She did not have any surgical history. Family history was positive for coronary artery disease and ovarian cancer. She has been married for the past 25 years, lived with her husband and three sons, all of them in good state of health. She has never smoked, used alcohol or illicit drugs and had no environmental exposures.

Vital signs on admission showed tachycardia of 110 bpm, tachypnoea of 22 bpm, oral temperature 98 F and physical examination was notable for bilateral vesicular breath sounds with minimal crackles at the bases. The remainder of the examination was normal and she had no inflammatory rashes or synovitis. Her laboratory work showed a white cell count of 6500 cells/mL, haemoglobin 11.5 mg/mL, haematocrit 40%, sodium 140 mEq/mL, potassium

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4.1 mEq/L, chloride 105 mmol/L, bicarbonate 26 mmol/L, BUN 12 mg/dL, creatine 0.8 mg/dL, ECG showed sinus tachycardia and a series of three troponins were less (0.01). Chest X-ray demonstrated an emphysematous pattern and pleuritis; CT angiogram of the chest did not show any signs suggestive of pulmonary embolism, no ground-glass pattern that would suggest *Pneumocystis pneumonia* (PCP), although it confirmed the pattern of emphysematous disease. Additional workup for chest pain was performed: stress echo was normal, without signs of inducible ischaemia. Finally, lung biopsy was performed and it confirmed the diagnosis of moderate LIP disease. The patient was started on methylprednisolone IV, hydroxychloroquine, acetylsalicylic acid (ASA) and respiratory nebulisers. Additional laboratory testing showed ANA (1:40) and positive anti-SS antigen (SSA) and anti-single side band (SSB). She had negative results for dsDNA, anticentromere, antiscleroderma-70 and α 1-antitrypsin; the complement was normal. At this point, the diagnosis of SS was made.

INVESTIGATIONS

- ▶ Dobutamine stress echo was ordered to evaluate chest pain, and it was negative for inducible ischaemia.
- ▶ The patient reported CBC and BMP (unremarkable), ANA (1:40) and positive SSA and SSB. She had negative results for dsDNA, anticentromere, antiscleroderma-70 and anti- α -trypsin; complement series was normal.
- ▶ A high-resolution CT of the chest disclosed emphysematous disease with multiple bronchial cysts, and diffuse interstitial infiltration was suggestive of LIP (figure 1).
- ▶ CT angio: negative for pulmonary embolism.
- ▶ Lung biopsy was performed and confirmed the diagnosis of moderate LIP disease (figures 2–4).

DIFFERENTIAL DIAGNOSIS

- ▶ Interstitial infiltrative pneumonia
- ▶ Pulmonary embolism
- ▶ Pleuritis
- ▶ PCP pneumonia
- ▶ Atypical chest pain/coronary artery disease

TREATMENT

The patient was started on intravenous methylprednisolone therapy, with a resolution of symptoms within 2 days. On the third day of hospitalisation, pulse therapy was discontinued and she was started on prednisone 50 mg daily with hydroxychloroquine as well. On the sixth day of hospitalisation, the dose of prednisone was decreased to 10 mg and she was discharged home.

OUTCOME AND FOLLOW-UP

The patient was started on pulse therapy initially with significant improvement of symptoms of cough and shortness of breath. Vital signs improved to normal limits, without any further episodes of fevers. The patient continued to improve and was discharged on day 6 of hospitalisation. She had a follow-up 6 months later. She denied any symptoms of SOB, cough or chest pain, therefore no further imaging studies or serologic tests were pursued and she continued to be managed clinically.

DISCUSSION

LIP is a clinicopathologic term that is related histologically to a dense interstitial infiltrate of the lungs by T and B cells, plasma cells and histiocytes.⁶ Its precise oetiology is unknown, but there are associations with those disorders that lead to

Figure 1 CT of the thorax demonstrating interstitial infiltration.

lymphocytic infiltration of tissues. This includes several autoimmune disorders such as SS, SLE, Hashimoto's disease,⁷ autoimmune haemolytic anaemia,⁸ chronic active hepatitis⁹ and primary biliary cirrhosis.⁷ Pulmonary involvement in SS varies widely, ranging from 9% to 75% depending on the detection method used, and it can be localised to small airways or diffuse with interstitial infiltration of the lungs.^{10 11} Only 1% of patients with primary SS presentation acquire LIP during the course of their disease.¹²

In adults, patients with LIP are usually women, with an average age at presentation of about 50 years. Presenting symptoms tend to be dyspnoea, cough, weight loss and chest pain. Its course can vary from the initial benign presentation, with response to steroid treatment, to complications such as superimposed infection, pulmonary fibrosis and lymphoma in the lung.

Other common causes associated to LIP are viral infections, such as HIV and Epstein-Barr virus, especially in children. The main differential diagnoses are lymphocytic infiltrative lung diseases such as pseudolymphoma, hypersensitivity pneumonia, non-specific interstitial pneumonia (NSIP) and a number of lymphoproliferative disorders such as small lymphocytic lymphoma, chronic lymphocytic leukaemia, plasma cell myeloma and lymphomatoid granulomatosis.¹³

Pulmonary manifestations of SS are common and include mucosal dryness secondary to glandular dysfunction; serositis with pleural effusions; interstitial lung disease; pulmonary

Figure 2 Lymphocytic aggregates around terminal airways.

Figure 3 Focal type 2 cell reactive hyperplasia.

hypertension; and the development of non-Hodgkin's lymphoma. Twenty-five per cent of patients with pSS are estimated to have pulmonary manifestations whose severity can range from mild to life threatening. Patients with sSS may have similar pulmonary involvement, though their severity is thought to be greater, possibly due to concomitant involvement of the lungs by the underlying primary connective tissue disease.

For the ILD associated with pSS, an open lung biopsy is the gold standard for diagnosis as bronchoscopy with lavage and CT imaging studies often produce non-specific findings.

The chest X-ray findings have characteristically described an interstitial lung disease pattern of reticular, coarse or fine reticulonodular shadowing.¹² Areas of cyst are poorly visualised or differentiated. Those are better visualised on the chest CT scan, which characteristically shows areas of ground-glass attenuation, poorly defined centrilobular and subpleural nodules.¹⁴ Other common findings include thickening of interlobular septum, lymph node enlargement and cystic dilated air spaces.¹⁴ Typically, a surgical lung biopsy or bronchoalveolar lavage (BAL) is required for diagnosis. These show an increase in the total T-cell and B-cell count¹⁵ with an interstitial pattern of involvement.

Microscopically, LIP is characterised by diffuse interstitial infiltrates composed of a polymorphic mixture of mature lymphocytes, plasma cells and histiocytes, which expand and widen the interlobular and alveolar septum.¹⁶ This helps to differentiate it from other lymphocytic diseases such as lymphoma which

Figure 4 Focal fibrosis and chronic inflammation underlying terminal airway.

show an isolated mass of monoclonal lymphocytes. The B lymphocytes are organised as granulomas in the parenchymal lung interstitium, forming germinal centres with positivity for CD20. T lymphocytes are also located in the interstitium, mixed with histiocytes and plasma cells. The staining of immunoglobulin light chains usually identifies the plasma cells.⁷

Corticosteroids are the traditional primary therapy, but other immunosuppressive agents such as cyclophosphamide, chlorambucil and azathioprine have been used with variable results.¹⁷ A recommended regimen is to use prednisone, 1.0 mg/kg/day for 8–12 weeks or until stabilisation.¹⁷ Then the dose is slowly tapered to 0.25 mg/kg/day and maintained for another 6–12 weeks. Approximately 50–60% of patients respond to corticosteroids with symptomatic or radiographic stabilisation or improvement.¹⁸ Others remain relatively stable for months or even years before they progress to pulmonary fibrosis and cor pulmonale, whereas some may turn into lymphomas or even die from their pulmonary disease within months.

The optimum therapy for LIP associated with pSS has not been well defined. Empiric therapy usually includes high-dose glucocorticoids along with a cytotoxic agent, commonly azathioprine. Cyclophosphamide has been used in a number of case reports, as the tumour necrosis factor (TNF) antagonists infliximab and etanercept and the anti-B-cell monoclonal antibody rituximab, but the numbers are too small to draw definitive conclusions on their relative efficacy.^{19 20}

Although SLE can manifest in the lungs, our patient did not present either with other symptoms or laboratory features of a lupus flare. Kim *et al*²¹ has reported a case of a 29-year-old man with respiratory symptoms as initial presentation diagnosed with pSS and LIP by lung biopsy. The case was successfully treated with pulse therapy. Our case illustrates a middle age woman with previous diagnosis of SLE, presenting with clinical and serological features of SS; workup for differential causes of chest pain and shortness of breath such as angina, pulmonary embolism and PCP included stress test and CT angiogram of the chest and were negative; lung biopsy was remarkable for LIP. Nevertheless, sSS with LIP is not common and there are no reports in the literature which make our case unique and interesting.

Learning points

- ▶ Pulmonary manifestations in autoimmune are common but variable depending on the underlying rheumatic disease.
- ▶ Lung interstitial pneumonia (LIP) is a very rare condition that is very rare as initial clinical manifestation of the Sjogren's syndrome.
- ▶ For challenging cases with rare disease presentation, the clinical laboratory data as well as histopathological analysis from lung biopsy are essential tools for establishing the final diagnosis.
- ▶ Treatment with systemic corticosteroids generally results in clinical improvement, though long term complications, including lung fibrosis and lymphoma may be seen.

Contributors All the authors were involved on patient care and manuscript writing.

Competing interests None.

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