Bronchiolitis Obliterans Organizing Pneumonia Associated with Cytomegalovirus Infection in a Patient with Systemic Lupus Erythematosus

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Introduction

Bronchiolitis obliterans organizing pneumonia (BOOP) has been categorized in the past two decades as a distinct clinicopathologic entity.1 The main clinical features include subacute onset of cough, fever, dyspnea, sparse crackles on chest auscultation and multiple patchy, often migratory, alveolar opacities on chest imaging. The characteristic histologic feature is the presence of buds of granulation tissue in the distal airspaces. BOOP has been causally related to various conditions such as drugs, infections, collagen vascular diseases, malignancies and radiation therapy.2 However, in the majority no specific cause can be detected. These idiopathic cases have the most favorable prognosis.

In this report, we describe a patient with Systemic lupus erythematosus, who developed BOOP secondary to Cytomegalovirus (CMV) infection.

A 48 year-old man, non-smoker, presented to our hospital with a 15-day history of fever, dry cough and progressively increasing shortness of breath. He had been diagnosed as a case of Systemic lupus erythematosus (SLE) with lupus nephritis 6 months ago and was on maintenance dose of Prednisolone (10-mg/day) and Cyclophosphamide (50-mg/day). Before presenting to us he had already taken 2 courses of broad-spectrum antibiotics.

Physical examination revealed tachypnea, fever (temperature 38oC) and diffuse bilateral end-inspiratory crackles on chest auscultation. Laboratory studies showed the following values: Hemoglobin 10.3g/dl; WBC count 10,100/cmm3, blood urea nitrogen 49mg/dL; creatinine 1.8mg/dL; alanine aminotransferase (ALT) 82 IU. Arterial blood gases revealed pH, 7.48; PaCO2 36.2 mmHg and PaO2 63.3mmHg.

A chest roentgenogram showed bilateral alveolar infiltrates denser in the lower zones (Figure 1). A high resolution CT chest also confirmed chest X-ray findings (Figure 2). Bronchoscopy was unremarkable. Bronchoalveolar lavage was negative for any microorganism. Blood cultures were also negative. He was started on imipenem and diflucan, along with 100mg of hydrocortisone every 6 hours, but his symptoms worsened over the next 3 days and

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he was transferred to the ICU requiring noninvasive ventilation (NIV).

Subsequently open lung biopsy was performed. Histological analysis of a biopsy specimen showed the presence of extensive patchy changes characterized by plugging of bronchioles with polypoidal fibroblasts mixed

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with fibrinous exudates and organization, extending into alveolar ducts and peribronchiolar alveolar spaces Figure 3). The alveolar septa and bronchiolar walls were thickened and contained an interstitial infiltrate of mononuclear inflammatory cells. The features were consistent with BOOP. There were no viral inclusions or fungal elements identified.

Serological assays revealed high titers of antibodies (both IgM and IgG) to CMV, Gancyclovir was added to the regimen.

Pulse steroid therapy with intravenous Methyl prednisolone 1 gm/ day was given for 3 days followed by oral Prednisolone 60 mg/day. The patient's condition improved dramatically with normalization of arterial blood gasses within days. The dose of Prednisolone was tapered gradually and at 3 months follow up he has no subjective complaint and chest roentgenogram findings have remarkably improved.

Discussion

Bronchiolitis obliterans organizing pneumonia (BOOP) was described in 1985 as a distinct entity, with different clinical, radiographic, and prognostic features than the airway disorder obliterative bronchiolitis.1 Idiopathic BOOP is the most common type.2 Postinfectious BOOP can develop after a variety of infectious pneumonias, including agents such as Chlamydia, Legionella and Mycoplasma pneumoniae and viruses such as Parainfluenza virus and Adenovirus. Parasitic infections such as malaria and fungal infections, including Cryptococcus neoformans and Pneumocystis carinii, have also been reported as a cause of BOOP.3 Cytomegalovirus pneumonia-associated BOOP has only been described in lung transplant recipients.4 To our knowledge, no previously reported case has described the development of BOOP in SLE patient due to CMV pneumonia.

BOOP associated with connective tissue diseases is clinically similar to the idiopathic form and has been reported with lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, and dermatomyositis. The process often responds to corticosteroid therapy, unlike the fibrotic process that may occur in these disorders.5 In our patient SLE was under control on maintenance steroid doses and was a less likely cause of BOOP.

Men and women are affected equally in most series of BOOP and are usually between 50 and 60 years (with a range from about 20 to 80).3 The onset of symptoms is subacute with fever, non-productive cough, malaise, anorexia, and weight loss. Haemoptysis, bronchorrhoea, chest pain, arthralgia, and night sweats are uncommon. Dyspnoea is usually mild but may occasionally be severe in some acute and life threatening cases.6 Mild hypoxaemia at rest and/or on exercise is common. Severe hypoxaemia in BOOP may reflect widespread and severe pulmonary disease or shunting in more limited lesions, or both. 3

There are no specific laboratory findings in BOOP. The erythrocyte sedimentation rate and C reactive protein levels are increased, with the erythrocyte sedimentation rate being >60 mm / 1 hour in about 30% of patients.6,7 There is a moderate leucocytosis, with an increased proportion of neutrophils.

The chest radiograph typically shows bilateral patchy (alveolar) infiltrates as in our case, cavities and effusions are rare. Generally, the infiltrates gradually enlarge from their original site or new infiltrates appear as the clinical course progresses; however, "migratory or mobile" pulmonary infiltrates have been reported in 10% to 25% of patients. 1,6,8

The chest computed tomographic (CT) scan shows bilateral areas of consolidation and ground glass opacities, usually with a predominant peripheral location.1,9 The CT scan in our case was also compatible with these findings.

Bronchoalveolar lavage (BAL) may be used to exclude other disorders or causes of BOOP, particularly infections. In our case BAL was negative for any microorganism although we did not perform viral culture. The differential white cell count may show a characteristic "mixed pattern" with increased lymphocytes. The lymphocyte CD4/CD8 ratio is decreased. 3,10

The video-assisted thoracoscopic lung biopsy is the preferred method for establishing a diagnosis. In our case the diagnosis of BOOP was also made on lung biopsy. Transbronchial lung biopsy specimens may show organising pneumonia in some cases but they do not adequately allow the exclusion of associated lesions or disclose clues to a cause for the process. 1,3,11

The diagnosis of BOOP relies on typical pathological and clinicoradiological features. On histopathological examination the lung specimen shows intra-alveolar buds of granulation tissue associated with fibroblasts, myofibroblasts, and loose connective tissue. The buds may extend from one alveolus to the next through the pores of Kohn giving a rather characteristic "butterfly" pattern. The lung structure is not disorganized. Bronchiolar lesions consist of similar plugs of granulation tissue inside the airway lumen in continuity with lesions in the alveoli and with limited inflammation in the bronchiolar wall.3,12 In our case, histopathological features were very much consistent with BOOP. The IgM and IgG titers of CMV on serum serology were very high and a presumptive diagnosis of concomitant CMV infection was made.

Prednisone, with its potent anti-inflammatory property, continues to be the recommended first-line agent for patients with symptomatic and progressive disease. The dosage is generally 1 mg/kg (60 mg/d) for 1 to 3 months, then 40 mg/d for 3 months, then 10 to 20 mg/d or every other day for a total of 1 year.1 Cytotoxic drugs, Cyclophosphamide and Azathioprine, are occasionally used to treat steroid resistant cases. 13

BOOP might recur in one third of patients on discontinuation of steroids. Recurrent BOOP can be successfully treated with the previously responsive dosage level of prednisone. 1,2

In conclusion BOOP is a condition seen in patients

with a variety of lung diseases. As this case demonstrates, CMV infection must be added to the list of infectious conditions associated with BOOP. A diagnosis based on examination of tissue samples and early initiation of corticosteroid therapy are essential to improve the outcome for patients with BOOP.

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