Bronchiolitis Obliterans–Organizing Pneumonia in a Renal Transplant Patient

Michele Marie McMahon, MD
Robert A. Promisloff, DO

Bronchiolitis obliterans–organizing pneumonia (BOOP) is a syndrome characterized by distinct clinical and pathologic features. It was first described in the early 1900s and affects men and women of all ages. The pathogenesis is not well understood but likely represents an exaggerated immune response to acute lung injury. BOOP typically has an acute or subacute presentation and has characteristic radiographic patterns. The etiologies of BOOP are diverse, but regardless of the underlying cause, most cases are responsive to steroids. This case report describes a renal transplant patient who presented on different occasions with 3 distinct radiographic patterns of BOOP. The causes, features, and treatment of BOOP are discussed.

CASE PRESENTATION
Initial Presentation and History
A 59-year-old man with a past medical history of hypertension, hyperlipidemia, diabetes mellitus, and end-stage renal disease was admitted to the hospital with complaints of fever to 101°F (38.3°C), fatigue, shortness of breath, and dry cough. The patient had a renal transplant 3 years prior to presentation. The patient had reported vague symptoms of shortness of breath for the past 8 months, but he noted that the symptoms had worsened over the past several weeks. He reported dyspnea with walking up a flight of stairs. He denied chills, night sweats, weight loss, anorexia, wheezing, hemoptysis, chest pain, paroxysmal nocturnal dyspnea, orthopnea, edema, nausea, vomiting, abdominal pain, or urinary symptoms. His medications on admission included cyclosporine 50 mg twice daily, amlodipine 10 mg once daily, prednisone 5 mg once daily, metoprolol 50 mg in the morning and 100 mg in the evening, sertraline 50 mg once daily, iron sulfate 325 mg 3 times/day, atorvastatin 20 mg once daily, doxazosin 2 mg every night, sirolimus 4 mg once daily, and an insulin pump. The patient had previously worked as a blacksmith and in a foundry. He admitted to smoking one half pack of cigarettes per day for the past 45 years but denied alcohol or drug use. The patient’s family history was significant for a brother who had pulmonary fibrosis.

Physical Examination
Vital signs on admission revealed a temperature of 97°F (36.1°C), pulse of 70 bpm with regular rhythm, respiratory rate of 18 breaths/min, and blood pressure of 130/78 mm Hg. His physical examination was unremarkable. Initial laboratory data showed a leukocyte count of 6.2 × 10^3/mm^3, with an unremarkable differential. The hemoglobin was 10.5 g/dL, the platelet count was 174 × 10^3/mm^3, and his electrolytes were within normal limits. He had a blood urea nitrogen level of 47 mg/dL and serum creatinine level of 2.1 mg/dL. His cyclosporine level was 97 ng/mL. Prothrombin time and partial thromboplastin time were within normal range. Results of liver function tests were also within normal limits. A urinalysis showed a specific gravity of 1.020 with proteinuria, 2–5 leukocytes and 0–2 erythrocytes per high power field, and was negative for nitrites and leukocyte esterase.

Laboratory and Imaging Studies
Blood cultures obtained during the hospitalization were negative, and a sputum culture showed normal oropharyngeal flora. The chest radiograph showed mild interstitial changes versus congestive heart failure. An electrocardiogram on admission showed normal sinus rhythm with evidence for left ventricular hypertrophy and no ischemic changes. The patient also had a 2-dimensional echocardiogram that showed normal left ventricular systolic function. The patient had a normal stress test within the year that noted no ischemic...
changes. Pulmonary function tests were obtained and revealed a mild restrictive defect with severely reduced diffusion capacity of carbon monoxide. A chest computed tomography (CT) scan was performed and showed interstitial changes most prominent in the periphery of the lung with focal areas of ground glass opacity at the lung bases (Figure 1). Results of laboratory tests for erythrocyte sedimentation rate, antinuclear antibody, rheumatoid factor, and angiotensin-converting enzyme levels were within normal limits. The prednisone dose was increased to 60 mg daily, and the patient had significant clinical improvement shortly thereafter.

Continued Clinical Course

The patient subsequently underwent an open lung biopsy which revealed foci of BOOP with lymphocytic infiltrate in the alveolar septae. Staining for bacteria, fungi, and acid-fast bacilli were negative. No evidence of viral cytopathic effect was present. At this point, the patient continued to improve clinically on steroids and was to continue on prednisone 60 mg daily with plans for a follow-up chest CT in the next month.

The following month, the patient again reported feeling short of breath. He now complained of productive cough and upper respiratory infection symptoms. He was readmitted for further evaluation. His physical examination at this time was remarkable for bilateral crackles. Laboratory data obtained during this hospitalization were within normal limits. A repeat chest CT scan revealed multiple nodular opacities scattered diffusely throughout the lungs (Figure 2), which were not evident on the previous CT scan from the patient’s first hospitalization (Figure 1). There were vague basilar ground glass opacities which had been noted on the previous CT. There was a suspicion that these lung findings could be due to an opportunistic infection.

The patient subsequently underwent bronchoscopy with bronchoalveolar lavage (BAL), which revealed many alveolar macrophages with occasional multinucleated giant cells, reactive bronchial cells, and a mixed inflammatory infiltrate. Respiratory cultures for viruses, bacteria, fungi, and acid-fast bacilli were negative. Specific cultures for varicella, cytomegalovirus, Legionella pneumophila, and Pneumocystis carinii were negative as well. The patient was subsequently taken to the operating room and underwent a repeat open lung biopsy as well as right middle lung wedge resection. Lung biopsy results again noted BOOP with no evidence for infection with stains for bacteria, fungi, and acid-fast bacilli as well as for viral cytopathic effect. There were no postoperative complications, and the patient remained clinically stable, requiring only 2 L nasal cannula oxygen (oxygen saturations, 92%–96%). He was subsequently discharged home with plans to continue prednisone that was tapered to 40 mg daily. There was some suspicion that the immunosuppressant sirolimus may have caused BOOP in this patient. This medication was discontinued, and the patient was started on azathioprine and continued on the other previously mentioned medications (ie, cyclosporine, amlodipine, prednisone, metoprolol, sertraline, atorvastatin, and doxazosin).

The patient continued to improve over the next
Within the bronchial lumens that extend into alveolar ducts and alveoli, BOOP has been reported in both men and women aged 20 to 70 years, but it most commonly occurs in individuals between 40 and 60 years. Smoking has not been found to be a risk factor for the development of BOOP.

BOOP is categorized as either idiopathic or secondary. Causes of secondary BOOP include infections, drugs, toxins, connective tissue diseases, immunologic disorders, malignancy, radiation therapy, bone marrow/lung transplantation, chronic thyroiditis, inflammatory bowel disease, and alcoholic cirrhosis (Table). In the case patient, there was clinical suspicion for an infectious etiology, especially given the history of immunosuppression. No clear infectious etiology was identified; however, viral-induced BOOP may be difficult to prove diagnostically. Adenovirus has been reported as a common viral etiology of BOOP, and in the current case, the presence of multinucleated giant cells in the BAL may be consistent with this diagnosis. Other systemic causes were ruled out by the patient’s history and laboratory data.

The immunosuppressant drug sirolimus was implicated as a possible cause of BOOP in the case patient and was subsequently discontinued. Sirolimus is a macrolide lactone isolated from the actinomycete streptomyces hygroscopicus. The mechanism of action of the drug is not completely understood, but it is believed to work by preventing T-lymphocyte activation by interfering with interleukin-2 signal transduction. The main reported side effects of the drug include hyperlipidemia, thrombocytopenia, and increased liver function tests.

**DISCUSSION**

**Etiology and Clinical Manifestations**

BOOP is an inflammatory disorder characterized histologically by the presence of granulation tissue within the bronchial lumens that extends into alveolar ducts and alveoli. BOOP has been reported in both men and women aged 20 to 70 years, but it most commonly occurs in individuals between 40 and 60 years. Smoking has not been found to be a risk factor for the development of BOOP.

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**Figure 3.** High resolution chest computed tomography scan of the case patient demonstrating focal areas of ground glass opacification, patchy bilateral densities, and a new pleural-based density at the right lung base.

**Figure 4.** Light microscopic section of the open-lung biopsy from the case patient. The specimen shows masses of granulation tissue, which fill the air spaces and small airways. A chronic inflammatory infiltrate is also present (trichrome stain, low magnification).
function enzymes. However, some recent studies have also reported pulmonary complications, including BOOP. In addition, 3 cases of interstitial pneumonia were recently reported in renal transplant patients receiving sirolimus. In all 3 cases, the pneumonia resolved upon discontinuation of the drug. The case patient did present a third time with pathologic evidence of BOOP after sirolimus was discontinued; therefore, a clear association between sirolimus and BOOP cannot be made in this case.

BOOP typically presents acutely or subacutely as a flu-like illness with nonproductive cough and exertional dyspnea. Anorexia and weight loss may be present, but hemoptysis is rare. The physical examination findings are usually unremarkable with the exception of crackles. Laboratory data can be normal but may also show leukocytosis. An elevated erythrocyte sedimentation rate has also been reported in many cases of BOOP. Pulmonary function tests typically show a restrictive picture with reduced vital capacity and a decreased diffusion capacity. An obstructive component is usually not seen unless the patient also has a significant smoking history.

BOOP has distinct radiographic features. This case is exceptional in that this patient exhibited 3 different radiographic patterns of BOOP on 3 separate occasions. Radiographically, the most common finding in BOOP is bilateral patchy infiltrates. A smaller percentage of patients may present with nodular opacities. BOOP may also present on imaging as a solitary focal lesion, but cavitation and pleural effusions are rarely seen. Additional CT findings include areas of consolidation with air bronchograms, ground glass opacities, reticulonodular interstitial infiltrates, peribronchial nodules, and absence of honeycombing. “Feeding vessels,” or vessels leading to the areas of consolidation, may be identified.

**Diagnosis**

The diagnosis of BOOP is best made by open lung biopsy. BAL findings for BOOP are nonspecific; however,
BAL may be used to identify underlying infectious etiologies. The most common finding on BAL is a mixed inflammatory infiltrate with a predominance of lymphocytes and smaller numbers of neutrophils and eosinophils.\(^1\)\(^2\)\(^3\)\(^4\) Pathologically, BOOP appears as buds of granulation tissue and inflammatory cells within the small airways extending to the alveolar ducts and alveoli. Honeycombing and fibrosis are absent, and there is no disorganization of the underlying lung architecture.\(^9\)

**Treatment**

Corticosteroids are the mainstay of treatment for BOOP. The usual starting dose is 1 mg/kg daily, which is continued for 3 months and then slowly tapered.\(^1\)\(^2\)\(^9\) Treatment duration varies, but corticosteroids are typically continued for at least 6 to 12 months. Because relapses can occur, patients may need to continue on an extended course of low-dose corticosteroids. The response to corticosteroids is good, and the majority of patients respond to the treatment. Low-dose erythromycin at a dose of 600 mg daily has been found to have anti-inflammatory properties and has also been used successfully to treat cases of BOOP.\(^3\)\(^12\) In addition, other immunosuppressive agents (eg, cyclophosphamide, azathioprine) have been utilized when patients do not respond to corticosteroids; however, data on the effectiveness of these agents are limited.\(^2\) Although the majority of cases of BOOP have an indolent course with a good prognosis, a small subset of patients may develop progressive respiratory failure and death.\(^9\)\(^12\)\(^13\) Risk factors for this life-threatening variant have not been clearly identified; however, it has been found that early initiation of corticosteroids may reduce mortality in this population.\(^15\)

**CONCLUSION**

This case presents a range of the clinical and radiographic features of BOOP. In the case patient, there were no clearly identified infections, drugs, or systemic etiologies; however, viral-induced BOOP can be a diagnostic challenge and should be considered as a possible etiology in this case. Regardless of the underlying etiology of BOOP, corticosteroids are the standard treatment. In addition, other immunomodulatory agents such as erythromycin, azathioprine, and cyclophosphamide can be effective in patients who cannot tolerate or do not respond to corticosteroids. The majority of patients with BOOP will have rapid improvement following the initiation of corticosteroids; however, there is a small percentage of patients who exhibit a fulminant course that may progress to respiratory failure and death. As this case demonstrates, a slow taper of corticosteroids may be necessary in order to prevent disease relapse. **HP**

**REFERENCES**