Bronchiolitis Obliterans Organizing Pneumonia Associated with Acute *Mycoplasma pneumoniae* Infection

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A patient with bronchiolitis obliterans organizing pneumonia (BOOP) associated with acute *Mycoplasma pneumoniae* infection is described. Although mycoplasmas have occasionally been associated with bronchiolitis obliterans, to the best of our knowledge, this is the first well-documented case of BOOP associated with *M. pneumoniae* infection. The diagnosis of BOOP was made by open-lung biopsy after fiberoptic transbronchial biopsy proved nondiagnostic. Corticosteroid therapy was administered and a dramatic improvement was observed; the patient remained without complaints during a 3-year follow-up period.

Bronchiolitis obliterans organizing pneumonia (BOOP) is a potentially reversible histopathologic condition seen in the lung either as an idiopathic clinical syndrome or as a nonspecific reaction to injury in a variety of situations, including infections [1]. Mycoplasmas have a wide range of immunomodulatory effects and have previously been associated with bronchiolitis obliterans (BO) without organizing pneumonia [2–4]. A causal relationship has also been suggested in experimental studies [5]. However, the component of organizing pneumonia was lacking in all these reports. To our knowledge, we report the first well-documented case of BOOP associated with *Mycoplasma pneumoniae* infection.

**Case Report**

A 57-year-old woman was admitted to the hospital because of a 10-day history of cough, low-grade fever, and exertional dyspnea. Physical examination revealed tachypnea, fever (temperature, 37.7°C), and diffuse crackles in both lungs. Laboratory studies disclosed the following values: *P*O$_2$, 61 mm Hg; *P*CO$_2$, 36 mm Hg (measured while the patient was breathing room air); hemoglobin, 13.5 g/dL; WBC count, 13,900/mm$^3$ (72% neutrophils, 6% band forms, and 1% eosinophils); and erythrocyte sedimentation rate, 100 mm/h. A chest roentgenogram revealed a segmental consolidation in the lower right lobe and an alveolar infiltrate in the upper left lobe (figure 1).

Blood cultures, a tuberculin skin test, Ziehl-Neelsen staining of three sputum samples, and cultures of three sputum samples on Löwenstein-Jensen medium were negative. Pulmonary function tests showed a mild restrictive defect: forced volume capacity, 2.07 L; forced expiratory volume in 1 second, 1.50 L (68% and 65%, respectively, of expected values). A high-resolution CT scan showed bilateral airspace consolidations in the upper and middle right lobes and in the upper left lobe in association with hilar lymphadenopathies (1 cm in diameter). A 2-week course of therapy with erythromycin and cefonicid was administered. Serological assays revealed no diagnostic rise in titers of antibody to Epstein-Barr virus, cytomegalovirus, *Legionella pneumophila* (serogroups 1–6), *Coxiella burnetii*, or *Chlamydia*. Antibodies to *M. pneumoniae* were clearly documented by an IgG ELISA: first titer (at admission), 1.05; second titer (4 weeks later), 2.95; ratio of second-to-first titers, 2.81 (seroconversion is defined by a ratio >1.64) [6].

Fever (temperature, 37.3°C), exertional dyspnea, dry cough, and a high erythrocyte sedimentation rate (80–92 mm/h) persisted. A chest roentgenogram obtained 1 month later revealed the persistence of bilateral, mainly peripheral, migratory patchy infiltrates in areas that were affected during the first admission (figure 2). The control WBC count was 7,900/mm$^3$, with 948 eosinophils/mm$^3$. The patient was admitted again, and fiberoptic bronchoscopy was performed. Samples obtained with a telescoping plugged catheter were cultured, but no aerobic bacteria or *Legionella* were isolated. Cytological examination of the bronchoalveolar lavage fluid did not reveal any malignant cells or infectious agents, and the percentage of inflammatory cells was unremarkable.

Transbronchial biopsy was also performed, but an insufficient amount of pulmonary tissue was obtained to establish a diagnosis. Open-lung biopsy was then performed. Histological analysis of a biopsy specimen showed the presence of patchy changes characterized by immature polypoid plugs of fibroblastic tissue within respiratory bronchioles with organization in alveolar ducts and peribronchiolar alveolar spaces (figure 3). The alveolar septa and bronchiolar wall within the areas of intraluminal fibrosis were thickened and contained an interstitial infiltrate of mononuclear inflammatory cells.

Therapy with oral prednisone (1 mg/[kg·d]) was administered for 1 month; this treatment resulted in a dramatic improvement in the patient’s condition, with normalization of the arterial blood gas levels and the chest roentgenogram findings.

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The dose was then tapered, and prednisone therapy was stopped 6 months later; during a 3-year follow-up period, the patient had no complaints, and chest roentgenographic findings were unremarkable.

**Discussion**

BOOP is usually idiopathic but has been associated with a variety of infections including those due to *Nocardia asteroides*, *Cryptococcus neoformans*, HIV, and many respiratory viruses [1, 7]. Although infections due to *Haemophilus influenzae*, *Bordetella pertussis*, *L. pneumophila*, and *C. burnetii* have also been associated with BOOP [8], a biopsy-proven case definitively associated with these pathogens has never been reported. This discordance may largely be due to the confusion that exists between the European and the American terminologies for BOOP [7].

Most investigators, however, essentially agree with the interpretation of Colby et al. [8] and Epler [9], which defines the BO component of BOOP as a proliferative BO lesion with a diffuse infiltrative lung disorder that is responsive to corticosteroid therapy. To the best of our knowledge, cases of biopsy-proven BOOP with intraluminal organization of persistent alveolar exudate by fibroblasts (thus defining organizing pneumonia [7]) secondary to *M. pneumoniae* infections have not been previously reported.

*Mycoplasma* has been associated, however, with constrictive bronchiolitis in some patients without the component of BOOP [1, 4, 10]. Although reports are scarce, in one by Epler et al. [1], the patient had many subsequent bacterial infections; these investigators could not firmly state that mycoplasma infection was the cause of BO but only that there was an association. Of interest, Coultas et al. [4] described a patient with biopsy-proven BO associated with the suspicion of *M. pneumoniae* infection that was based only on the finding of a high titer of cold agglutinins. In fact, a review of their figures suggests that BOOP could have been present in their patient, even though the researchers did not use this term in their description of the pathology. However, the connective tissue filling in that case was mainly confined to the small airways without organizing pneumonia, spirometry showed a severe obstructive defect without restriction, and the diagnosis of mycoplasma infection could not be confirmed by serology (CF titers) or by immunofluorescent staining of lung tissue. Furthermore, many viruses...
can induce cold agglutinins and could have been the etiology of that case. Finally, in a third report [10], acute *M. pneumoniae* infection was associated with BO, again without organizing pneumonia.

A causal relationship between mycoplasma infection and BO (without organizing pneumonia) has also been suggested in experimental studies with dogs [5]. Many immunologic extra-pulmonary complications associated with acute viral infections (cold hemagglutinin—associated hemolytic anemia, myopericarditis, Stevens-Johnson syndrome, and transverse myelitis) also have subsequently been identified in cases of mycoplasma infections [9, 11]. In fact, mycoplasmas share many features with viruses and have a wide range of immunomodulatory effects [2, 12]. Therefore, it should not be surprising that BOOP, largely associated with infections with many viruses and with immunologic conditions, could also be triggered by mycoplasma infections.

Our patient had biopsy-proven BOOP. Furthermore, her excellent response to corticosteroid therapy strongly argues against the diagnosis of constrictive BO, usually an irreversible airway disorder [2, 13]. The diagnosis of mycoplasma infection—related slowly organizing pneumonia (mimicking slowly organizing viral pneumonia) can be discarded on the basis of the histological findings and the absence of spontaneous recovery without steroid therapy [1].

BOOP is a common nonspecific reaction seen in patients with a variety of unrelated lung diseases. As this case demonstrates, *M. pneumoniae* infection must be added to the list of infectious conditions associated with BOOP, even in the presence of organizing pneumonia. Although it should be a rare complication, mycoplasma infection is a frequent condition in young people, and clinicians must be aware of this possibility when patients have complicating mycoplasma pneumonia. BOOP is a syndrome characterized by an indolent course and favorable prognosis; however, fulminating and life-threatening variants of this syndrome have recently been reported [13]. A diagnosis based on examination of tissue samples and early initiation of corticosteroid therapy are essential to improve the outcome for patients with BOOP.

### References