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**Mycoplasma pneumoniae-Associated Bronchiolitis Causing Severe Restrictive Lung Disease in Adults***

Report of Three Cases and Literature Review

Edward A. Chan, MD; Tul Kalayanamit, MD; David A. Lynch, MD; Rubin Tuder, MD; Patrick Arndt, MD; Robert Winn, MD, FCCP; and Marvin I. Schwarz, MD, FCCP

**Study objectives:** To characterize adult Mycoplasma pneumoniae-induced bronchiolitis requiring hospitalization.

**Design:** We encountered an adult patient with severe bronchiolitis in the absence of pneumonia due to M pneumoniae. To determine the relative frequency of such a condition, we retrospectively reviewed the medical records of adults over a 4-year period with a hospital discharge diagnosis of “bronchiolitis” from a university hospital.

**Setting:** University Hospital of the University of Colorado Health Sciences Center, Denver, CO.

**Study subjects:** From 1994 to 1998, 10 adult inpatients were identified with a diagnosis of bronchiolitis. There were two with respiratory bronchiolitis, one with panbronchiolitis, one patient with bronchiolitis obliterans organizing pneumonia (BOOP), and six with acute inflammatory bronchiolitis. Including the initial patient, three had a definitive clinical diagnosis of Mycoplasma-associated bronchiolitis.

**Results:** The three adult patients with bronchiolitis due to M pneumoniae are unusual because they occurred in the absence of radiographic features of a lobar or patchy alveolar pneumonia. Hospital admission was occasioned by the severity of symptoms and gas exchange abnormalities. One patient had bronchiolitis as well as organizing pneumonia (BOOP) that responded favorably to corticosteroid treatment. The other two had high-resolution CT findings diagnostic of an acute inflammatory bronchiolitis. One of the patients with inflammatory bronchiolitis had an unusual pattern of marked ventilation and perfusion defects localized predominantly to the left lung. All three had restrictive ventilatory impairment on physiologic testing.

**Conclusions:** In adults, Mycoplasma-associated bronchiolitis without pneumonia is rarely reported, but in hospitalized patients, it may be more common than expected and may be associated with severe physiologic disturbances.

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**Key words:** bronchiolitis; bronchiolitis obliterans organizing pneumonia; constrictive bronchiolitis; infectious bronchiolitis; inflammatory bronchiolitis; Mycoplasma pneumoniae

**Abbreviations:** BOOP = bronchiolitis obliterans organizing pneumonia; HRCT = high-resolution CT; PCR = polymerase chain reaction

A number of pulmonary complications have been reported to occur with *Mycoplasma pneumoniae* infection. These include pneumonia, tracheobronchitis, obliterative bronchiolitis, bronchiectasis, pneumatocele formation, MacLeod-Swyer-James syndrome, pleural effusion, interstitial fibrosis, lung abscess, and exacerbation or possibly initiation of reactive airway disease.1–11 Small airways disease (bronchiolitis) in the form of an inflammatory bronchiolitis, constrictive bronchiolitis obliterans, or bronchiolitis obliterans organizing pneumonia (BOOP) also occurs.12–14 Bronchiolitis due to *M pneumoniae* usually accompanies a bronchopneumonia. Readily recognized in pediatric patients, documented infectious bronchiolitis in adults is unusual.15,16 Herein we describe three adult patients with bronchiolitis due to *M pneumoniae* and review the literature concerning small airways disease caused by infectious agents in adults, with particular emphasis on *M pneumoniae*.

**Materials and Methods**

Patients with a hospital discharge diagnosis of bronchiolitis, from April 1, 1994 to April 1, 1998, were identified from the University Hospital discharge database of the University of Colorado Health Sciences Center. A retrospective chart review was performed to identify those with a diagnosis of *M pneumoniae*-associated bronchiolitis.
RESULTS

Ten adult patients were identified with a physician discharge diagnosis of bronchiolitis. Of these, three had a definitive diagnosis of *M. pneumoniae*-associated bronchiolitis. All three were previously healthy adults who presented with acute small airways disease due to *M. pneumoniae* but without the radiographic features of lobar or patchy alveolar infiltrates that are characteristic of *M. pneumoniae* pneumonia. One patient had BOOP and two had an acute inflammatory bronchiolitis. All had significant restrictive lung disease and gas exchange abnormalities. Two were treated with corticosteroids and had a favorable response.

CASE REPORT

Case 1

A previously healthy nonsmoking 39-year-old man complained of 10 days of progressive dyspnea and a productive cough. He also reported nausea, one episode of vomiting, and watery diarrhea for 3 days. On examination, his temperature was 37.7°C, pulse rate was 87 beats/min, BP was 120/70 mm Hg, and respiratory rate was 22 breaths/min. Physical examination was notable for moderate respiratory distress and bilateral crackles. The chest radiograph demonstrated a fine nodular interstitial pattern (Fig 1). A room air arterial blood gas revealed a pH of 7.43, Pco2 of 36 mm Hg, Po2 of 41 mm Hg, and an oxygen saturation of 78%. The peripheral WBC count was 9.4 × 10^9/L, with 61% neutrophils, 24% lymphocytes, and 12% monocytes. Treatment with IV erythromycin and trimethoprim-sulfamethoxazole was initiated. Sputum culture revealed mixed flora. Blood cultures were negative. On hospital day 3, due to the lack of improvement, he underwent a video-assisted thoracoscopic biopsy of the left lower lobe and lingula. This revealed extensive proliferative (exudative) bronchiolitis with organizing pneumonia consistent with BOOP (Fig 2). Microbiological staining and cultures of the tissue were negative. The acute serum cold agglutinin titer was 1:512 and the *M. pneumoniae* IgG (complement fixation) was 1:64. The IgM antibody for *M. pneumoniae* was 1:2,560. Convalescence titers for cold agglutinin and IgM were negative. A regimen of IV methylprednisolone was started, 250 mg every 6 h, and the regimen of erythromycin was continued. The patient was discharged from the hospital on hospital day 11 to complete a 3-week course of erythromycin, 500 mg four times daily, and prednisone, 50 mg once daily. Pulmonary function at hospital discharge revealed an FEV1 of 2.03 L (54%), FVC of 2.74 L (59%), FEV1/FVC of 74%, thoracic gas volume of 2.26 L (66%), residual volume of 1.05 L (66%), and total lung capacity of 3.57 L (56%), consistent with severe restrictive lung disease. After 1 month, a chest radiograph revealed only minimal linear scarring at the left lung base. At 5 months, the FEV1 improved to 2.67 L (69%), FVC to 3.52 L (68%), and FEV1/FVC was 76%. Prednisone dosage was tapered over 9 months, guided by improvement in the patient’s symptoms and reduction of oxygen requirements.

Figure 1. Chest radiograph of patient 1, demonstrating a fine nodular interstitial pattern, especially at the bases.

Case 2

A 46-year-old previously healthy nonsmoking man complained of upper respiratory tract symptoms for 1 week. This was followed by a nonproductive cough, dyspnea, bilateral pleuritic chest pain, and fevers for 2 days prior to hospital admission. On examination, he was in mild-to-moderate respiratory distress. His temperature was 38.0°C, pulse rate was 120 beats/min, BP was 122/74 mm Hg, and respiratory rate was 24 breaths/min. There were markedly diminished breath sounds throughout the left lung with scattered bilateral crackles. A room air arterial blood gas revealed a pH of 7.47, PaCO2 of 31 mm Hg, PaO2 of 55 mm Hg, and an oxygen saturation of 88%. The chest radiograph was normal. Treatment with IV ceftriaxone, 1 g every 12 h, and erythromycin, 500 mg every 6 h, was initiated. A ventilation-perfusion lung scan revealed a marked decrease in both ventilation and perfusion on the left (Fig 3). On the right, there were several matched ventilation and perfusion defects. A pulmonary arteriogram was normal. Pulmonary function testing revealed FEV1 of 1.87 L (43%), FVC of 2.44 L (44%), FEV1/FVC ratio of 77%, functional residual capacity of 1.85 L (50%), residual volume of 1.64 L (74%), total lung capacity of 4.19 L (54%), and diffusion capacity for carbon monoxide corrected for alveolar volume of 6.88 ml/min/mm Hg/L (127%), consistent with a severe restrictive defect. The high-resolution CT (HRCT) scan revealed fine centrilobular nodules throughout the left lung (Fig 4). A similar pattern was observed in the superior segment of the right lower lobe consistent with an inflammatory bronchiolitis. Gram’s stain, routine bacterial and fungal cultures, and viral cultures of BAL fluid were negative. Sputum cytology and BAL fluid were negative for viral inclusion bodies. A polymerase chain reaction (PCR) determination for *M. pneumoniae* from the BAL fluid was positive. PCR amplification was performed at the Diagnosti Virology Laboratory at the University of Colorado School of Medicine and was based on a method previously described.12 The pair of primers used were MP4A (5’-AGG CTC AGG TCA ATC TGG CGT GGA-3’) and MP4B (5’-GGA TCG AAC AGA TCG GTG ACT GGG T-3’), both of which are specific for the *M. pneumoniae* PI adhesion gene. Once the results of the PCR were known, prednisone, 60 mg/d, was added to the erythromycin regimen, with significant improvement in the patient’s symptoms.

Case 3

A 64-year-old man with well-controlled type 2A diabetes mellitus presented with a 6-week history of shortness of breath, cough intermittently productive of yellow sputum, chest pain, and sore throat. He was a never-smoker. He was treated with cefaclor 1 week prior to hospital admission, without relief. On examination, his temperature was 37.1°C, pulse rate was 106
beats/min. BP was 158/80 mm Hg, and respiratory rate was 22
breaths/min. On lung examination, there were bilateral crackles
and inspiratory squawks. There was no clinical evidence of
myocardial dysfunction. Room air arterial gas revealed a
pH of 7.39, a PaCO₂ of 36 mm Hg, a PaO₂ of 44 mm Hg, and an
oxygen saturation of 79%. Chest radiograph demonstrated a mild
increase in interstitial markings with perilobular thickening.
HRCT of the chest revealed multiple tiny and indistinct nodular
opacities with a branching pattern (“tree in bud’) in the periphery,
consistent with bronchiolitis (Fig 5). In addition, scattered
areas of ground-glass opacities were present bilaterally. A ven-
tilation-perfusion lung scan showed multiple ventilatory defects
that were either greater than or matched to perfusion defects. A
spirometry revealed an FEV₁ of 1.17 L (52%), FVC of 1.40 L
(36%), and an FEV₁/FVC ratio of 83%. Sputum culture grew
Legionella pneumophila
and a convalescent titer obtained 3 weeks later was 1:16. The level of
IgG fell from 260 to 170 U/mL during the same
period. The patient was treated with azithromycin, with progres-
sive improvement of his symptoms.

Bronchiolitis is subdivided according to specific histo-
logic features. Infectious bronchiolitis is an acute, cellular
bronchiolitis with epithelial necrosis, inflammation of the
bronchiolar walls, and an intraluminal exudate.32,33 Prolif-
erative bronchiolitis, characteristically seen in the setting
of BOOP, consists of polyoid masses of new granulation
tissue (Mason’s bodies) within the lumina of bronchioles
and alveolar ducts, often extending into the alveolar
spaces.34 In addition, there is an interstitial cellular re-

Figure 2. Left, A: lung micrograph of patient 1 showing granulation tissue (Mason’s body, arrow),
projecting into a respiratory bronchiule through the site indicated by the dashed arrow (pentachrome,
original magnification ×200). Note the presence of mucus more proximally in the bronchiolar lumen. Right, B: granulation tissue cast filling an alveolar duct (arrow). Note the presence of branching cast of
granulation tissue (Masson’s bodies) within the lumina of bronchioles (hematoxylin-eosin, original magnification ×400).

Discussion

Bronchiolitis refers to an inflammatory disease primar-
ily involving the terminal and respiratory bronchioles, but
in some cases, extending to the adjacent alveolar ducts and
alveolar spaces.18,19 The histologic appearance of bronchi-
olitis includes an inflammatory (cellular) bronchiolitis,
constrictive bronchiolitis obliterans, or a proliferative
bronchiolitis.20,21 Known causes of bronchiolitis include
toxic fume inhalation, tobacco smoke, mineral dust inha-
lation, penicillamine, collagen vascular diseases, and infec-
tions.22–26 Bone marrow, heart-lung, and lung transplanta-
tion have also been associated with this complication.27–29
Clinically apparent infectious bronchiolitis is generally
considered to be a pediatric disease, rarely being recog-
nized in adults.16 Although most pediatric cases are asso-
ciated with respiratory syncytial virus, other viruses such as
parainfluenza, influenza, rhinovirus, rubeola, mumps, par-
vovirus, enterovirus, coronavirus, coxsackie virus, and vari-
cella zoster are occasionally isolated.35,19 In adults, there
are occasional reports of viral- or bacterial (M pneumoniae
and Legionella pneumophila)-induced bronchiolitis.4,30,31

Selected Reports
which lung tissue was available for examination, findings were more consistent with fatal asthma with evidence of mucus plugging of primary and secondary bronchi, basement membrane thickening, marked eosinophilic infiltration, and Leyden crystal deposition. In another patient, an acute obstructive defect with hyperinflation, a diffuse and fine granular pattern on chest radiograph, and a cold agglutinin titer of 1:1,024 were found, consistent with constrictive bronchiolitis due to either a viral or Mycoplasma infection. Constrictive bronchiolitis with obstructive physiologic condition was also described in an adult with varicella pneumonia. O’Reilly described an adult with bronchiolitis due to parainfluenza type 2. Despite a normal chest radiograph, there was significant hypoxemia and hypercarbia. Although symptoms and moderate airflow obstruction improved with bronchodilator and corticosteroid treatment, airflow limitation persisted. Seggev et al reported three cases of bronchiolitis obliterans in which detailed physiologic studies were available. One, a 69-year-old nonsmoking woman, developed a postviral respiratory illness characterized by shortness of breath, airflow limitation, and hypoxemia. Open lung biopsy specimen revealed narrowing of the bronchiolar lumina due to subepithelial deposition of fibrous connective tissue. Although the airway obstruction initially improved with corticosteroid therapy, the patient developed refractory respiratory failure and died. Both the histopathologic condition and the lack of significant improvement with corticosteroids in this patient are consistent with a diagnosis of constrictive bronchiolitis obliterans.

It is unusual to see the pattern of BOOP following infection. A 28-year-old woman developed fatal respiratory failure as a result of a progressive acute interstitial pneumonitis. Autopsy indicated a proliferative bronchiolitis (BOOP) with connective tissue plugs within the lumina of respiratory bronchioles that extended to the alveolar ducts and alveoli. Moreover, the presence of multinucleated giant cells and smudge cells suggested adenovirus as the etiologic agent. In a previously healthy elderly man with subacute Nocardia asteroides pneumonia, lung biopsy specimen revealed extensive proliferative bronchiolitis. His condition improved after treatment with trimethoprim-sulfamethoxazole alone.

Figure 3. Top: Posterior view of 99mTc-DTPA aerosol ventilation scan of patient 2 showing severely reduced ventilation to the left lung, with a more patchy decrease in ventilation of the right lung. Bottom: corresponding image of 99mTc-MAA perfusion scan shows matching areas of decrease in perfusion.

Figure 4. HRCT scan of patient 2, retargeted to the left lung, shows fine centrilobular nodules (arrows) compatible with an inflammatory bronchiolitis.
Pyogenic bacteria causing bronchiolitis without an associated pneumonia, to the best of our knowledge, has not been described. Goldstein et al described BOOP in four patients with nosocomial *Serratia marcescens* pneumonia. However, in all cases, the BOOP reaction was not the predominant feature but rather accompanied a necrotizing bronchopneumonia. Sato et al described a case of bronchiolitis resulting from *L. pneumophila*, diagnosed by a fourfold rise in indirect fluorescent antibody titer. The patient presented with radiographic bilateral diffuse infiltrates and severe hypoxemia that dramatically responded to corticosteroids. Based on the pathologic description of the polypoid masses of intraluminal connective tissue and the favorable response to corticosteroids, this lesion should be classified as BOOP. Miyagawa et al described two elderly patients with postinfectious BOOP. One had serologic evidence of *L. pneumophila* infection and the other, *M. pneumoniae* infection. Interestingly, circulating immune complexes were found in both patients prior to treatment with corticosteroids and were undetectable after treatment. A 57-year-old woman was recently reported to have BOOP due to *M. pneumoniae* infection. Similar to our patient 1 with BOOP, there was significant improvement with corticosteroid treatment. In a patient with IgA deficiency due to ataxia-telangiectasia, BOOP occurred due to *M. pneumoniae* infection.

Rollins and coworkers described six patients with open lung biopsy specimen-proved inflammatory (cellular) bronchiolitis due to *M. pneumoniae*. In three of the cases, there was an accompanying bronchopneumonia. A lymphoplasmocytic bronchiolar wall infiltrate with a neutrophil-rich intraluminal exudate was present. Ultrastructurally, there was extensive injury to the respiratory mucosa, causing loss of cilia and ciliated cells. Also noted was edema, fibrosis, and plasma cells infiltrating the bronchial and bronchiolar walls with extension of the inflammatory exudate from the bronchiolar lumens into the alveolar spaces. This histologic pattern is distinct from both constrictive bronchiolitis and BOOP. Although most patients with acute infectious inflammatory bronchiolitis recover without significant sequelae, some may develop constrictive bronchiolitis or reactive airways disease. Based on this and the few reports of constrictive bronchiolitis evolving from BOOP, we speculate that acute inflammatory bronchiolitis could also be an earlier stage of proliferative bronchiolitis (BOOP). Fraley et al described a patient with respiratory failure from *M. pneumoniae* pneumonia who had both acute necrotizing pneumonitis with consolidation and “bronchiolitis obliterans” on open lung biopsy specimen. Although the type of bronchiolitis was not described further, the restrictive changes noted on pulmonary function tests would argue against constrictive bronchiolitis obliterans and would be more representative of BOOP or inflammatory bronchiolitis. In another patient with respiratory failure due to *M. pneumoniae*, a nodular infiltrate on chest radiograph correlated with a lung biopsy specimen that showed a confluent infiltrate in a bronchiocentric distribution. The inflammatory infiltrate consisted of plasma cells, lymphocytes, macrophages, and neutrophils in addition to basophilic connective tissue obliterating the lumen of the small airways and alveolar ducts. Pulmonary function testing in this patient revealed a mixed obstructive and restrictive defect.

The aforementioned clinical cases correlate with a hamster model of *M. pneumoniae* infection, in which intratracheal inoculation of the organism produced a bronchiolitis characterized by peribronchial and perivascular lymphocytic infiltrate and a neutrophil and macrophage exudate in the bronchiolar lumen. Thus, it is likely that cases of severe pulmonary infections caused by *M. pneumoniae* are due to an exuberant cell-mediated immune response, accounting for the favorable response to corticosteroids in the cases cited above.

Herein we describe three adults with *M. pneumoniae* pulmonary infections who presented with small airways disease as their only manifestation. One (patient 1) had postinfectious bronchiolitis with organizing pneumonia (BOOP), and two had an acute inflammatory bronchiolitis. Although patient 1 had BOOP, his chest radiograph was atypical. Patients 1 and 3 had subtle findings on chest radiograph despite severe gas exchange abnormalities, and patient 2 had striking ventilatory and perfusion defects despite a normal chest radiograph. These cases are unusual because both BOOP and inflammatory bronchiolitis are uncommon presentations of *M. pneumoniae* infections, especially in the absence of lobar or patchy alveolar pneumonia. Moreover, acute infectious bronchiolitis requiring hospitalization is unusual in adults. In patient 1, open lung biopsy specimen demonstrated a proliferative bronchiolitis. The restrictive physiology, crackles on lung examination, and response to corticosteroids in this individual are consistent with the diagnosis of BOOP. Although it is possible that constrictive bronchiolitis may follow BOOP, this patient, after 2 years of follow-up, has not developed progressive airflow limitation. One notable finding in patient 2 was the marked asymmetric and

![Figure 5. HRCT scan of chest of patient 3 shows diffuse centrilobular nodularity (*tree in bud* appearance, arrow) consistent with inflammatory bronchiolitis.](image-url)
extensive involvement by bronchiolitis of the left lung, as evidenced by physical examination, ventilation-perfusion lung scanning, and HRCT. The bronchiolitis present in patients 2 and 3 is not consistent with either constrictive bronchiolitis obliterans because of the lack of obstructive physiology or of BOOP based on the HRCT scan, but it rather is characteristic of an inflammatory (cellular) bronchiolitis.29 The HRCT findings are similar to other inflammatory bronchiolar diseases such as diffuse panbronchiolitis.32 In two of the patients in whom full pulmonary physiologic testing was done, severe restrictive lung disease was present in both patients. Although restrictive physiologic condition is to be expected in the patient with BOOP,18 we postulate that the matched ventilatory and perfusion defects that were present in the left lung of the second patient with inflammatory bronchiolitis indicated a poorly functioning left lung, resulting in low lung volumes. The third patient did not have lung volumes measured, but the FEV1 to FVC ratio of > 100% predicted suggests a restrictive pattern.

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Negative Pressure Pulmonary Hemorrhage*

David R. Schwartz, MD; Anjli Maroo, MD; Atul Malhotra, MD; and Howard Kesselman, MD

Negative pressure pulmonary edema, a well-recognized phenomenon, is the formation of pulmonary edema following an acute upper airway obstruction (UAO). To our knowledge, diffuse alveolar hemorrhage has not been reported previously as a complication of an UAO. We describe a case of negative pressure pulmonary hemorrhage, and we propose that its etiology is stress failure, the mechanical disruption of the alveolar-capillary membrane.

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Key words: negative pressure pulmonary edema; pulmonary hemorrhage; stress failure

Abbreviations: ITP = intrathoracic pressure; NPPE = negative pressure pulmonary edema; NPPH = negative pressure pulmonary hemorrhage; OSA = obstructive sleep apnea; Pms = mean systemic pressure; Ppc = pulmonary capillary hydrostatic pressure; Ppi = pulmonary interstitial hydrostatic pressure; Ptm = pulmonary capillary transmural pressure; UAO = upper airway obstruction

Formation of noncardiogenic pulmonary edema has been anecdotally observed following various forms of upper airway obstruction (UAO), with one series in adults describing an incidence as high as 11%.1 The principal physiologic mechanism underlying the formation of edema in this setting involves the generation of markedly negative intrathoracic pressure leading to a net increase in the pulmonary vascular volume and the pulmonary capillary transmural pressure (Ptm). We report a case of an adult man who suffered diffuse alveolar hemorrhage following an acute UAO. We postulate that the mechanism underlying negative pressure pulmonary hemorrhage (NPPH) is stress failure of the alveolar-capillary membrane caused by the marked elevation of pulmonary capillary wall tension. Decreases in pericapillary interstitial pressure might contribute significantly to the development of stress failure in NPPH.

CASE REPORT

A 46-year-old muscular African-American man with a medical history significant for high myopia, glaucoma, mild mental retardation, and cocaine abuse underwent elective vitreous debride ment and cataract removal for scarring due to bleb-associated endophthalmitis of his right eye. Preoperative testing was not performed. General anesthesia was induced with propofol and fentanyl and was maintained with isoflurane and nitrous oxide. The patient was given succinylcholine prior to an atraumatic endotracheal intubation, and mivacurium was used for the intraoperative paralysis. Clear bilateral breath sounds were noted, and the capnography trace was normal. The surgery proceeded uneventfully with normal intraoperative hemodynamic and respiratory indexes. The patient received 2 L of lactated Ringer’s solution, and his urinary output totaled 480 mL over 4 h.

At the end of the procedure, peripheral twitch monitoring showed 4/4 twitches with a train-of-four, and the patient met the standard criteria for extubation without the need for neuromuscular blockade.

*From the Pulmonary and Critical Care Unit (Drs. Schwartz, Malhotra, and Kesselman) and Department of Medicine (Dr. Maroo), Massachusetts General Hospital, Boston, MA. Manuscript received May 8, 1998; revision accepted October 27, 1998.

Correspondence to: David R. Schwartz, MD, Pulmonary and Critical Care Unit, Massachusetts General Hospital, 55 Fruit Street, Bulfinch-148, Boston, MA 02114-2696; e-mail: schwartz@massmed.org