

A 43-Year-Old-Woman with Nonresolving Pneumonia

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CASE PRESENTATION

Initial Presentation and History

A 43-year-old woman presented to the emergency department with dry cough and dyspnea on exertion. Three months prior to this presentation, the patient presented to her primary care physician for a flu-like illness with recurring episodes of fatigue and myalgias without fever, weight loss, or night sweats. Initial chest radiograph ordered by the primary care physician revealed bilateral lower lobe infiltrates. The patient was diagnosed with community-acquired pneumonia and was given multiple courses of antibiotics, which did not improve her symptoms. Repeated chest radiographs over 3 months demonstrated that the bilateral lower lobe infiltrates had not resolved. The patient's dyspnea progressively worsened over 6 weeks following a course of oral antibiotics.

Patient Evaluation

In the emergency department, physical examination revealed a temperature of 97.9°F (36.6°C), respiratory rate of 18 breaths/min, blood pressure of 165/85 mm Hg, heart rate of 92 bpm, and oxygen saturation of 95% without supplemental oxygen. No lymphadenopathy was found. Chest auscultation revealed bilateral crackles. Abdominal examination was normal, and there was no lower extremity edema. Results of serum chemistry studies and the white blood cell count were normal. The patient was admitted to the hospital for further work-up.

Blood culture and sputum culture were negative. A chest radiograph showed bilateral infiltrates. Computed tomography (CT) of the chest showed bilateral patchy air-space consolidation with air bronchograms predominantly in the lower lung lobes and without mediastinal lymphadenopathy (**Figure 1**). All results from serologic evaluation for vasculitis and immunologic diseases were negative. Analysis of bronchial lavage specimens showed no bacterial or viral infection and no malignant cells. Bronchoscopy with transbronchial

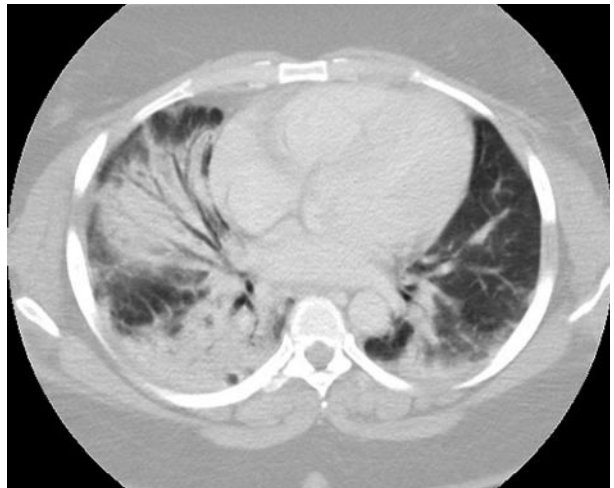


Figure 1. Computed tomography scan of the chest demonstrating bilateral air-space consolidations.

lung biopsy was performed; evaluation of the specimens revealed intra-alveolar plugs of granulation tissue composed of inflammatory cells and myxoid connective tissue (**Figure 2**). Viral inclusions were absent. Cultures for acid-fast bacilli, viruses, and fungi were negative.

WHAT IS YOUR DIAGNOSIS?

- (A) Acute respiratory distress syndrome
- (B) Cryptogenic organizing pneumonia
- (C) Lupus pneumonitis
- (D) Pulmonary tuberculosis
- (E) Sarcoidosis

At the time this manuscript was submitted, Dr. Hadid was a third-year resident, Department of Medicine, John H. Stroger Jr. Hospital of Cook County, Chicago, IL. He is now an attending physician (hospitalist), Rush Copley Medical Center, Aurora, IL. Dr. Tulaimat is an attending physician, Division of Pulmonary and Critical Care, John H. Stroger Jr. Hospital of Cook County, and an assistant professor, Rush Medical College, Chicago, IL.

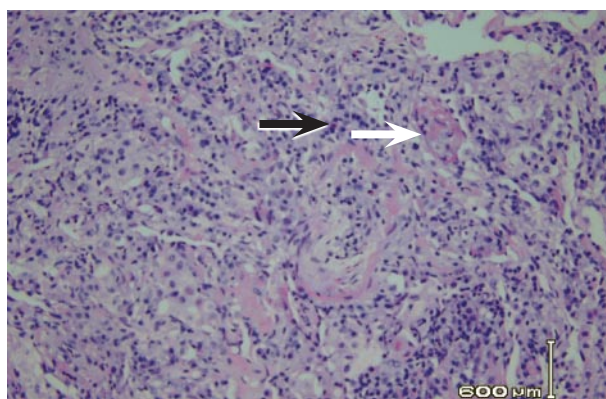


Figure 2. Specimen obtained by bronchoscopy with transbronchial lung biopsy demonstrating intra-alveolar plugs of granulation tissue composed of inflammatory cells (black arrow) and myxoid connective tissue (white arrow).

ANSWER

The correct answer is (B), cryptogenic organizing pneumonia (COP).

DISCUSSION

There are no clinical or pathologic features specific for COP. Rather, COP is a diagnosis of exclusion. In this patient, history, symptoms, and chest radiography suggested a diagnosis of community-acquired pneumonia, but symptoms had not resolved after multiple courses of antibiotics. The biopsy specimen from this patient showed foci of organizing pneumonia (Figure 2) and all other tests were negative. After all other causes of organizing pneumonia were ruled out (Table), the diagnosis of COP was made. Sarcoidosis was unlikely because granulomatous inflammation was absent, and tuberculosis was improbable because the culture for acid-fast bacilli was negative. Acute respiratory distress syndrome (ARDS) is an acute syndrome characterized by diffuse alveolar damage on biopsy; however, this patient demonstrated a subacute process and had no histologic findings that would support a diagnosis of ARDS. The patient did not have a history of lupus or clinical or laboratory findings typical of lupus; also, in contrast to COP, lupus pneumonitis is characterized by alveolar wall necrosis, hemorrhage, and hyaline membranes.¹

CRYPTOGENIC ORGANIZING PNEUMONIA

COP is a term used to refer to the idiopathic form of bronchiolitis obliterans organizing pneumonia (BOOP), a pulmonary inflammatory process characterized by polypoid endobronchial masses of myxoid fibroblastic tissue resembling granulation tissue that fill the distal alveolar spaces (organizing pneumonia) and extend into the

Table. Etiology of Secondary Bronchiolitis Obliterans Organizing Pneumonia

Infectious agents	Connective tissue and immunologic diseases
<i>Coxiella burnetii</i>	Systemic lupus erythematosus
Mycoplasma	Rheumatoid arthritis
Chlamydiae	Scleroderma
Legionella	Sjögren’s syndrome
<i>Pneumocystis carinii</i>	Polymyositis
Adenovirus	Dermatomyositis
HIV	Behçet’s syndrome
Cytomegalovirus	Other
Influenza virus	Radiotherapy
<i>Plasmodium vivax</i>	Organ transplant
Cryptococcus	Cocaine use
Drugs	Alcoholic cirrhosis
Minocycline	Chronic thyroiditis
Amiodarone	Inflammatory bowel disease
Phenytoin	Textile printing dye
Gold	Extrinsic allergic alveolitis
Hematologic disease	Anthrax vaccination
Myelodysplastic syndrome	
Lymphoma	

terminal bronchioles.² Despite the chronic inflammation in the alveolar walls, lung architecture is preserved.³ Although the pathophysiology of inflammatory processes involved in organizing pneumonia is still unclear, a recent report showed that overproduction of matrix metalloproteinase-9 and tissue inhibitor of metalloproteinase-1 occurred in COP.⁴ BOOP that is associated with infectious or noninfectious etiologies (Table)^{2,5–17} is referred to as secondary BOOP.

Rapidly progressive BOOP (either idiopathic or associated with other diseases) has been reported. Cohen et al¹⁵ reported 10 patients with rapidly progressive BOOP characterized by severe respiratory failure. All patients had characteristic histologic findings of BOOP, and 9 patients had associated diseases, including connective tissue diseases, chronic obstructive lung disease, asthma, hypothyroidism, and cancer. Unfortunately, there are no clear factors to predict which patients will develop progressive BOOP.

Clinical and Radiologic Manifestations

The most common symptoms of COP are nonproductive cough and dyspnea on exertion, observed in 80% and 64% of patients, respectively, in a recent study.¹⁸ Up to 50% of patients describe a prodrome of flu-like symptoms that manifest with fever, fatigue, and malaise. Crackles on chest examination are a common

physical finding. In a review of 45 patients with BOOP, 17 of 31 (55%) with COP presented with crackles.¹⁸ Isolated wheezes and a normal lung examination may be found in 2% and 28% of cases, respectively.²

There are no radiologic features specific for COP. Bilateral alveolar opacities with air bronchograms are the most frequent abnormalities seen on chest radiography.¹⁹ Recurrent or migratory pulmonary opacities are common,²⁰ and cavities and effusions occur in less than 5% of patients.²¹ The most frequent findings on chest CT are consolidations, which are usually seen in the subpleural or peribronchovascular regions.²² Other findings include a ground-glass pattern,²² small nodular opacities, and bronchial wall thickening and dilation.¹⁹ High-resolution CT may show nodules, nonseptal linear or reticular opacities, and bronchial dilation.²³ These findings may be seen in other interstitial lung diseases, especially chronic eosinophilic pneumonia. Conversely, honeycombing may be seen in chronic eosinophilic pneumonia but is unusual in COP. Pulmonary function testing shows a restrictive pattern and decreased diffusion capacity in 72% and 82% of patients, respectively.²

Diagnosis

Many diseases can mimic COP. Chronic eosinophilic pneumonia, bronchoalveolar carcinoma, interstitial lung diseases, and several diseases listed in the Table may have similar clinical and radiologic findings as well as show granulation tissue in the distal airways. Therefore, biopsy must show organizing pneumonia and all other causes of organizing pneumonia must be excluded (Table) before COP is diagnosed. Clinical, microbiologic, and serologic evaluation to rule out other causes should be followed by biopsy to confirm organizing pneumonia before initiating therapy. Biopsy specimens should be sent for cultures to rule out infectious causes of organizing pneumonia. Patients with COP are commonly misdiagnosed with community-acquired pneumonia, and COP should be considered if the pneumonia does not respond to therapy.

Findings on bronchial lavage are nonspecific for COP, but it may be helpful to perform culture and cytologic examination to exclude infectious and neoplastic causes of pulmonary consolidations. Transbronchial biopsy can be helpful if a large specimen is obtained and if the specimen shows all distinctive alveolar and bronchiolar organizing tissue.²¹ Secondary causes of BOOP can be missed by bronchoscopy; therefore, open lung biopsy and video-assisted thoracoscopy are still the gold standard for diagnosis of COP. Video-assisted thoracoscopy is preferred because of reduced mortality and length of hospital stay as compared with open lung biopsy.²⁴

Management

Corticosteroids are the first choice for treatment of COP. Although there is no clear-cut prednisone dose to be administered, a dose of 1 mg/kg daily (60 mg/day) for 4 to 12 weeks slowly tapered over 1 year (40 mg/day for 12 wk, then 10–20 mg/day thereafter) has been recommended.^{2,25} Methylprednisolone 250 mg intravenously every 6 hours for the first 5 days has been suggested for patients with rapidly progressive BOOP.¹⁵ Patients should be reevaluated every 8 weeks, and chest radiography should be performed at each visit. Recovery occurs in 65% to 80% of patients who receive corticosteroids.¹⁶ Azathioprine, cyclosporine, and cyclophosphamide were also reported to be effective.^{26–29} Cyclophosphamide should not be the medication of first choice due to its side effects.

COP can recur during treatment or after a complete course of prednisone. Relapse may occur more frequently in patients initially presenting with hypoxia³⁰ or if initial treatment is delayed.³¹ However, recurrence does not affect the outcome.³¹ Early recognition and treatment of COP can decrease relapse rates and may affect mortality in some cases. In 5 patients with fulminant COP, early recognition of BOOP and prompt initiation of corticosteroid therapy prevented mortality in 3 patients.³²

CLINICAL COURSE OF CASE PATIENT

The case patient was started on oral prednisone 60 mg/day and was discharged home. The dose of 60 mg/day was given for 3 months and was then tapered over the next 6 months to 10 mg/day. The patient improved clinically over the next year. No further radiologic evaluation was performed on this patient. **HP**

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