CLINICAL VIGNETTE

Shortness of Breath: Initial Presentation of Cryptogenic Organizing Pneumonia

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Case Presentation

A 57-year-old female with morbid obesity, anxiety disorder, type 2 diabetes mellitus, and Chiari malformation presented to the emergency room (ED) with acute on chronic shortness of breath with reduced exercise tolerance.

Her exertional dyspnea first began four months prior to presentation, which prompted outpatient evaluation including an echocardiogram showing mild diastolic dysfunction and pulmonary function testing revealing a moderate restrictive defect. The patient was initially managed conservatively without medications. However, over the past two weeks she noted a rapid worsening of her symptoms, experiencing dyspnea on exertion now after just 25 feet as opposed to two blocks previously. She also noted a productive cough, paroxysmal nocturnal dyspnea, and orthopnea. She denied chest pain, fevers, rhinorrhea, diarrhea, loss of smell or taste, weakness, or numbness. She was unvaccinated for COVID-19, denied sick contacts, and had a negative COVID-19 PCR test prior to ED presentation. Her family and social history were unremarkable. Due to her progressive symptoms, she presented for urgent evaluation.

On initial exam she was afebrile and normotensive, but had tachycardia with heart rate 120 BPM, and an oxygen saturation of 92% on room air, which improved to 96% with 2 liters oxygen via nasal cannula. She had decreased breath sounds on exam and some accessory muscle use but the remainder of her physical exam was unremarkable.

Her initial evaluation included a negative repeat COVID-19 PCR test and normal CBC, BMP, BNP, and troponin. EKG showed sinus tachycardia without ischemic changes. Her chest x-ray demonstrated bilateral interstitial opacities concerning for pulmonary edema versus interstitial pneumonia such as COVID-19. CT pulmonary angiogram did not reveal a pulmonary embolism but did show patchy bilateral peribronchovascular and peripheral airspace opacities of unclear etiology. Repeat echocardiogram was stable compared to prior.

Highest initial suspicion remained for COVID-19 infection in an unvaccinated individual, and she underwent a third repeat COVID-19 PCR test which was negative. She continued to feel dyspneic and required 2L of oxygen to maintain saturation above the low 90s. ESR and CRP were elevated to 75 9RR < 30mm/hr) and 86 (RR < 5mg/L) respectively. Further atypical infectious and rheumatologic testing returned negative including seasonal respiratory viral panel, procalcitonin, legionella, coccidioides, ANA, anti-CCP, RF, ANCA, and ACE.

Pulmonology was consulted and recommended bronchoscopy with biopsy. Her bronchoalveolar lavage (BAL) showed normal respiratory flora with negative BAL COVID-19 PCR, AFB testing, respiratory panel PCR, fungal culture, KOH testing, cryptococcus antigen, and galactomannan. However, her transbronchial biopsy revealed the diagnosis: Pathology report noted bronchial, bronchiolar, and alveolated lung with peribronchiolar inflammation, chronic pneumonitis, and focally increased foamy macrophages, suggestive of organizing pneumonia.

The patient was diagnosed with cryptogenic organizing pneumonia, given negative rheumatologic and infectious testing and absence of any offending medications. She was started on prednisone 60 mg daily for 4 - 6 weeks with a plan for slow steroid taper over 3 - 6 months. As of her last pulmonary clinic follow-up visit, she reported significant symptomatic improvement after completing a prednisone taper and was off oxygen.

Discussion

Cryptogenic organizing pneumonia (COP), formerly known as bronchiolitis obliterans organizing pneumonia (BOOP), is a subtype of interstitial lung disease (ILD) that is associated with characteristic inflammatory and fibrotic histologic features affecting the distal airspaces and alveoli.[1]

According to the American Thoracic Society (ATS) and European Respiratory Society (ERS), COP is classified as an interstitial idiopathic pneumonia (IIP) within the category of diffuse ILD. Other conditions that fall within IIPs include idiopathic pulmonary fibrosis, acute interstitial pneumonia, usual interstitial pneumonia (UIP), and nonspecific interstitial pneumonia (NSIP), among others. These conditions are essentially distinguished from one another based on differing histopathologic characteristics.[2]

While the exact pathophysiology of COP is still unknown, the prevailing notion is that COP occurs due to damage of the alveolar epithelium. This results in a leakage of plasma proteins, which causes an increase in fibroblasts, myofibroblasts, and fibrin formation within the alveolus.[1,3,4] Intra-alveolar fibro-inflammatory buds termed Masson's bodies are hallmarks of the disease.[1,3,4] Overproduction of matrix metalloproteinase

and dysregulation of vascular endothelial growth factor have also been postulated.[5]

Clinically, patients with COP can manifest with dyspnea, nonproductive cough, fever, and weight loss over an acute to subacute duration ranging from weeks to months, with physical exam typically revealing crackles without wheezing.[1,3,4] Most patients have some degree of hypoxemia with exertion as well as at rest. COP typically presents in patients from ages 40 – 60, and seldom affects children.[1,3,4]

Radiographic findings usually demonstrate bilateral ground glass opacities or consolidations in the peripheral and lower lung zones.[1,3,6] High resolution CT scan can reveal more detailed findings such as bronchial wall thickening and dilation and/or nodular opacities.[3,6] In patients with COP, pulmonary function tests confirm a restrictive ventilatory defect with reduced DLCO.[1,3] Consideration of organizing pneumonia often occurs after patients do not respond to an empiric course of antibiotics.

Importantly, COP is a diagnosis of exclusion. Organizing pneumonia, as observed histologically, can be caused by a multitude of other entities, most commonly by connective tissue/rheumatologic conditions and various drugs. A variety of rheumatologic conditions including polymyositis, dermatomyositis, Rheumatoid arthritis, Systemic lupus erythematosus, systemic sclerosis, and many others have been shown to cause organizing pneumonia. Additionally, multiple drugs including amiodarone, beta blockers, carbamazepine, cyclophosphamide, mesalamine, minocycline, phenytoin, and others have been implicated. Other conditions associated with organizing pneumonia, include malignancy, thyroiditis, infection (ranging from aspergillus, mycobacterium, legionella, mycoplasma and viral infections), heart failure, cryoglobulinemia, inflammatory bowel disease, inhalation injury, and organ transplantation.[1-4]

Given the wide array of conditions that can cause organizing pneumonia, evaluation should include testing for atypical organisms, laboratory testing to exclude rheumatologic conditions, as well as evaluation to exclude malignancy and other conditions. Careful review of medications should also be performed. A negative evaluation for secondary causes along with characteristic histopathologic findings are needed to diagnose COP.

Patients in whom COP is suspected undergo bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsy to assist with diagnosis. BAL may show increased lymphocytes, neutrophils and eosinophils as well as macrophages and mast cells,[1,4] but BAL usually provides greater utility in ruling in or out other conditions on the differential. In order to confirm characteristic histopathologic findings, patients may need surgical lung biopsy in order to obtain enough tissue sample for definitive diagnosis.

Treatment of COP involves a prolonged course of oral glucocorticoids. This recommendation is based upon clinical guidelines and observational studies as opposed to randomized controlled trials. Patients are maintained on oral prednisone for at least three to six months. After initiating 0.75 – 1 mg/kg prednisone dosing for four to eight weeks, patients may be gradually tapered with improvement in symptoms.[1,3] Patients can often relapse after initial glucocorticoid treatment, as studies have shown than greater than 50% of patients with COP relapse at some point following initial treatment.[1,3,7] Given the lengthy duration of corticosteroid treatment, patients should also be closely monitored for known adverse side effects of steroids. A minority of patients may develop fulminant disease and yet others may respond to therapy but require lifelong treatment with steroids to achieve control. Additionally, steroid sparing agents such as macrolide antibiotics, azathioprine, cyclophosphamide and mycophenolate mofetil have been used in some refractory cases of COP, but robust data regarding their efficacy in COP is limited.[1,3]

Compared to other known interstitial idiopathic pneumonias, COP fortunately has a favorable prognosis with complete clinical and radiographic improvement in over 60% of treated patients.[1,3,4] This is in stark comparison to secondary organizing pneumonia or other conditions such as idiopathic pulmonary fibrosis (IPF), where morbidity and mortality rates are much higher.[1,3]

Conclusion

Cryptogenic organizing pneumonia (COP) is an interstitial idiopathic pneumonia that is diagnosed based upon specific inflammatory histopathologic characteristics affecting the distal airspaces and alveoli and is a diagnosis of exclusion. Secondary causes of organizing pneumonia including drugs, rheumatologic conditions, infection, and malignancy, amongst others need to be ruled out prior to establishing a diagnosis of COP. Treatment involves a prolonged course of oral corticosteroids. Prognosis is favorable, as a majority of patients experience clinical and radiographic resolution of disease following treatment.

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