Interstitial Lung Disease in a 70-Year-Old Man with Ulcerative Colitis

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ABSTRACT

Interstitial lung disease is a rare but increasingly recognized extraintestinal manifestation of inflammatory bowel disease that can have devastating consequences if left untreated. We report a case of ulcerative colitis–associated interstitial lung disease presenting with acute hypoxic respiratory failure during an ulcerative colitis flare. Gastroenterologists and pulmonologists should be aware of the numerous bronchopulmonary signs and symptoms that can suggest systemic illness in inflammatory bowel disease.

INTRODUCTION

Interstitial lung disease (ILD) is an increasingly recognized extraintestinal manifestation of ulcerative colitis (UC) that results in increased shortness of breath, chronic cough, chest pain, and hypoxemia. The relevance of this association cannot be overstated as it serves as a significant source of morbidity and mortality in these patients. In addition, compared to healthy controls, patients with UC showed abnormal pulmonary function tests, whether symptomatic or not, more than 50% of the time. If diagnosed early, these symptoms can often improve or even resolve with steroid treatment.

CASE REPORT

A 70-year-old man presented with a UC flare. He reported a remote 20-pack-year smoking history and a 4-year history of left-sided UC managed with sulfasalazine and intermittent steroid and mesalamine enemas. Symptoms included diarrhea and hematochezia treated with systemic steroids due to cost constraints. Over the following months, the patient developed worsening of his previously mild chronic shortness of breath and dyspnea on exertion. He had known coronary artery disease and underwent a cardiac stress test to evaluate these symptoms. He experienced a syncopal event during the stress test and was subsequently admitted to the hospital. After admission, an echocardiogram and a left heart catheterization failed to explain his syncope. A computed tomography scan of the chest showed bilateral subpleural interstitial fibrosis in the presence of moderate centrilobular paraseptal emphysema (Figure 1). This was concerning for drug-induced lung disease, so sulfasalazine and mesalamine enemas were discontinued upon discharge from the hospital.

The patient continued to struggle with bowel urgency and hematochezia for another 2 months, and he was started prednisone 40 mg daily and received vedolizumab. A week after this treatment, he was again hospitalized with hypoxia requiring 6–10 L oxygen by nasal cannula. His labs were notable for normal chemistries and a normal complete blood count: white blood cells 10.47 k/mm³ (neutrophils 85.4%, lymphocytes 11.3%, and eosinophils 0.2%), hemoglobin 14.1, sedimentation rate of 36 mm/h, and C-reactive protein 6.8 mg/dL. A full rheumatologic panel including an antinuclear antibody revealed only a positive anti-LA antibody, and his pulmonary function tests showed marked reduction in diffusing capacity of the lungs for carbon monoxide. Bronchoscopy with a
bronchoalveolar lavage (BAL) showed a lymphocyte predominance of 60%, macrophages of 20%, and neutrophils of 8%. The BAL cultures showed mixed oropharyngeal flora without abnormal bacterial or fungal elements, as well as a negative viral polymerase chain reaction, so no clear infectious etiology was found. A repeat computed tomography scan of the chest showed significant interval worsening of fibrotic disease (Figure 2).

He was diagnosed with UC-related ILD with temporal worsening of respiratory status with UC exacerbation. There was a discussion of possible lung transplant, but his advanced age prevented him from being a candidate. His prednisone was increased to 60 mg daily and he started mycophenolate mofetil; his hypoxia became resistant to therapy, and he succumbed to his progressive respiratory failure.

DISCUSSION
This case demonstrates the natural history of an increasingly recognized extraintestinal complication of UC and treatment manifested as interstitial lung disease. Our patient had several years of inflammatory bowel disease (IBD), treated with sulfasalazine and occasional steroid or mesalamine enemas, and he gradually developed respiratory distress. His hypoxia seemed to plateau each time he received treatment for a flare, but his disease management became increasingly difficult as his lung disease continued to worsen. This is not surprising, as respiratory decompensation may accompany exacerbations of IBD but do not always correlate well with disease state, often preceding signs of bowel disease by years. However, symptoms of airway involvement often arise in patients with a long history of active IBD. This suggests that, while there does not have to be concurrent UC flare and respiratory distress, long-standing inflammation of the gut is generally associated with worsened inflammation in the lung.

Extraintestinal manifestations of IBD can affect 21–41% of all patients and can increase with duration of intestinal disease. In addition, they are a significant cause of morbidity and mortality in this patient population. Storch et al. reviewed more than 600 patients with UC and found that more than 50% showed abnormal pulmonary function tests compared to healthy controls, specifically a decrease in diffusing capacity of the lungs for carbon dioxide. This data implies that the incidence of IBD-associated ILD may be significantly underappreciated by gastroenterologists.

Large airway disease, particularly chronic bronchitis and bronchiectasis, is strongly associated with UC and typically presents after UC has been diagnosed. A chronic productive cough is generally noted, along with shortness of breath, chest pain, and wheezing; in some cases, bronchial dilatation can be seen on chest x-ray. Small airway disease is uncommonly described, but when present it is more commonly reported in young patients and is more commonly seen before the onset of IBD.

On bronchoscopy with BAL, the most typical findings are mucosal edema and hyperemia with mucosal hyperplasia. As with our patient, a non-specific but common finding is lymphocytic predominance, though cases of neutrophilia or eosinophilia have also been reported.

The pathogenesis of UC-associated ILD is poorly understood, but there are several theories as to the mechanism. Both the colonic and respiratory epithelia arise from the primitive foregut and contain submucosal lymphoid tissue that aid in host
This similarity could lead to similar reactions when exposed to external antigens. Furthermore, there may be an association with interleukins (IL-1 IL-2, IL-6) and tissue necrosis factor α (TNF-α). ILD can occur in UC ipso facto as well as from medications like sulfasalazine and mesalamine. Side effects can be either dose-related or idiosyncratic. Interstitial disease, as was seen in our patient, is the most common lung disease, and the pulmonary toxicity can often be reversed after withdrawal of the drug.

Prognosis is generally quite good, and findings of edema, cellular infiltrates, and granulation on BAL tend be most responsive to treatment. Bronchiectasis, fibrotic strictures, and deposits of fibrous material are poor prognostic markers for patients. Typical treatment is systemic steroids, usually at a dose of 0.5 mg/kg prednisone daily with gradual taper. Occasionally, as was the case with our patient, the fibrosis may be steroid-resistant, so treatment with cyclophosphamide, mycophenolate mofetil, or even anti-TNF agents like infliximab can be used.

Our patient had developed ILD related to his UC with pulmonary fibrosis that was resistant to increasing doses of systemic steroids and mycophenolate mofetil. While some cases spontaneously resolve, and many are responsive to steroids, our patient’s presentation did not improve despite escalation of therapy. This case illustrates the importance of high suspicion for ILD in patients with IBD who develop worsening shortness of breath, chronic cough, or hypoxia, and it also highlights the importance of early referral to pulmonology and treatment with systemic corticosteroids in this potentially fatal disease.

DISCLOSURES
Author contributions: HW Collins wrote the manuscript, reviewed the literature, and is the article guarantor. JW Frye edited the manuscript.

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REFERENCES
1. Butland RJ, Cole P, Citron KM, Turner M. Chronic bronchial suppuration and inflammatory bowel disease. J Med. 1981;50:63–75.
2. Storch I, Sachar D, Katz S. Pulmonary manifestations of inflammatory bowel disease. Inflamm Bowel Dis. 2003;9:104–15.
3. Spira A, Grossman R, Balter M. Large airway disease associated with inflammatory bowel disease. Chest. 1998;113:1723–6.
4. Desai SJ, Gephardt GN, Stoller JK. Diffuse panbronchiolitis preceding ulcerative colitis. Chest. 1989;95:1342–4.
5. Rankin GB. Extraintestinal and systemic manifestations of inflammatory bowel disease. Med Clin North Am. 1990;74:39–50.
6. Su GC, Judge TA, Lichtenstein GR. Extraintestinal manifestations of inflammatory bowel disease. Gastroenterol Clin North Am. 2002;31:307–27.
7. Rankin GB, Watts HD, Melnyk CS, Kelley ML. National cooperative Crohn’s disease study: extraintestinal manifestations and perianal complications. Gastroenterology. 1979;77:914–20.
8. Williams H, Walker D. Extraintestinal manifestations of inflammatory bowel disease. Ann Med. 2006;42:97–114.
9. Kužnar T, Sleiman C, Brugièrre O, et al. Severe tracheobronchial stenosis in a patient with Crohn’s disease. Eur Respir J. 2005;21:209–12.
10. Vandenplas O, Casel S, Delos M, Trigaux JP, Melange M, Marchand E. Granulomatous bronchiolitis associated with Crohn’s disease. Ann J Respir Crit Care Med. 1998;158:1676–9.
11. van Lierop PP, Samsom JN, Escher JC, Nieuwenhuis EE. Role of the innate immune system in the pathogenesis of inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 2009;48:142–51.
12. Higenbottam T, Cochrane GM, Clark TJ, Turner D, Millis R, Seymour W. Bronchial disease in ulcerative colitis. Thorax. 1980;35:581–5.
13. Sossai P, Cappellato MG, Stefani S. Can a drug-induced pulmonary hypersensitivity reaction be dose-dependent? A case with mesalamine. Mt Sinai J Med. 2001;68(3):389.
14. Shneerson JM. Lung bullae, bronchiectasis, and Hashimoto’s disease associated with ulcerative colitis treated by colectomy. Thorax. 1981;36 (4):313.
15. Hotermans G, Benard A, Guenanen H, Demarq-Delerue G, Malart T, Wallaert B. Nongranulomatous interstitial lung disease in Crohn’s disease. Eur Respir J. 1996;9:380–2.