CLINICAL VIGNETTE

Constrictive Bronchiolitis with Pulmonary Thrombosis Associated with Ulcerative Colitis

Corinne Tina Sheth, M.D., Patricia Eshaghian, M.D., and Russell Buhr, M.D.

Introduction

Pulmonary complications of inflammatory bowel disease (IBD) are well-described, including airway and interstitial lung disease, serositis, organizing and eosinophilic pneumonia, and venous thromboembolic disease (VTE). Abnormal pulmonary function tests (PFTs) without symptoms are also reported. Treatments can also cause lung disease. We present a case of IBD-associated constrictive bronchiolitis with associated in situ pulmonary thrombosis.

Case Presentation

A 52-year-old female former smoker was diagnosed with ulcerative colitis (UC) in 2013. Dyspnea began in 2014 and was presumed due to emphysema. She did not respond to inhalers, and her UC was poorly controlled with adalimumab and previously 5-ASA and 6-MP. Exam was notable for hypoxia. PFTs showed severe obstruction and air trapping (FEV1 27% predicted, FVC 53%, ratio 51%, DLCO 61%, and RV 167%). CTA chest did not show emphysema or VTE but suggested constrictive bronchiolitis. Surgical lung biopsy confirmed this and showed thick-walled pulmonary arteries with thrombus in two lobes (Figure 1). V/Q scan and venous Doppler ultrasound were negative. Echocardiogram was negative for pulmonary hypertension. Oral steroids were started in addition to adalimumab. Symptoms improved, diffusing capacity normalized, and oxygen requirements resolved. However, steroid taper initially failed. She was then optimized to an immunosuppressive regimen of infliximab, 6-mercaptopurine, and prednisone in addition to a respiratory regimen of tiotropium inhaler, fluticasone and salmeterol inhaler, montelukast, and azithromycin. This resulted in improvement to both UC and pulmonary symptoms. She is now nearly off steroids with continued improvement (Table 1).

Discussion

Both the colonic and respiratory epithelia share an embryonic origin from the primitive foregut. They have similar mucosal immunity and can similarly be sensitized to pathogens, which may be a common target of inflammation at both epithelial sites.[1,2,3] Nearly half of the cases of airway involvement in IBD occur post colectomy, perhaps due to the focus of inflammation switching from the gastrointestinal tract to the lung after surgery.[1] This suggests that ongoing bowel inflammation is not a prerequisite for pulmonary involvement. Pulmonary involvement can be present at the time of diagnosis of IBD or years after the onset of bowel disease and can be present during active disease or independent of disease activity.[2]

While one study reported the incidence of pulmonary complications in IBD at 0.21%,[1] the true prevalence remains unknown. The diagnosis can be difficult to establish particularly in patients who have respiratory symptoms prior to bowel symptoms and in patients who smoke. Additionally, some patients have pulmonary function abnormalities without symptoms, so there are likely many patients with IBD and asymptomatic pulmonary involvement who are undiagnosed.[2] While most extra-intestinal manifestations are more common in Crohn's disease, pulmonary involvement in Crohn's disease is rare. Pulmonary involvement is more commonly seen associated with ulcerative colitis.[2,3]

PFT abnormalities are frequently found in patients with IBD without the presence of any respiratory symptoms or lung radiograph findings. While all abnormalities including obstructive disease, restrictive disease, bronchial hyper-responsiveness, and hyperinflation can be seen, the most common is a decrease in the diffusing capacity of the lung for carbon monoxide (DLCO) seen in about half of patients with IBD. Identifying these asymptomatic abnormalities may lead to early recognition of a steroid responsive respiratory disease.[2]

The most common pulmonary manifestation of IBD is large airways disease with inflammation and suppuration. Bronchiectasis is the most common, often occurring days to weeks after colectomy. Chronic bronchitis is the second most common. Symptoms of both include chronic productive cough that does not respond to antibiotics. Rarely large airways disease can include severe tracheal inflammation and obstruction comprised of glottic or

subglottic stenosis and tracheal inflammation and stenosis. Symptoms include coughing, dysphonia, stridor, hoarseness, and shortness of breath. Inhaled and/or oral corticosteroid therapy has been reported as effective though dosage, duration, and route of therapy remains empiric.[2]

Our patient had ulcerative colitis associated constrictive bronchiolitis, which is a small airways disease. This is less commonly reported and often occurs in isolation from large airways disease. It is often seen earlier in the course than large airways disease and prior to the onset of IBD. It is now diagnosed more frequently due to increased utilization of high resolution CT chest scans. Findings include bronchial wall thickening, mucoid impaction, centrilobular ground glass nodules, and, most notably, mosaic attenuation due to air trapping that is most accentuated in expiratory views.[2,3,4]

The term *constrictive bronchiolitis* was first used to describe lesions characterized by diffuse submucosal and peribronchiolar fibrosis without accompanying fibroblastic proliferation. This leads to concentric narrowing of the bronchiolar lumens and eventual luminal obliteration. Symptoms include dyspnea and functionally there is significant airflow obstruction. The disease is chronic and slowly progressive. The pathologic changes are considered to be irreversible.[4]

Constrictive bronchiolitis is usually refractory to inhaled steroids and response to oral steroids is considered slight to moderate.[2] There have been case reports of constrictive bronchiolitis after lung transplant and in bone marrow transplant associated graft-versus-host disease that suggest a benefit from a regimen of fluticasone, montelukast, and azithromycin.[5] This may be extrapolated to treatment of ulcerative colitis associated constrictive bronchiolitis. Lung transplantation has been required in some cases. Surgery of the colon may aggravate airways disease and is not recommended for treatment.[2]

Lung parenchymal disease associated with IBD is relatively uncommon. Lung parenchymal disease associated with IBD includes cryptogenic organizing pneumonia, eosinophilic pneumonia, and non-specific interstitial pneumonitis. Rarely, necrobiotic and granulomatous pulmonary nodules have also been reported. Lung parenchymal disease generally has a marked response to steroids (inhaled, oral, or intravenous depending on type and severity) though at times cyclophosphamide or infliximab may be needed. Other rare associations include pleural or pericardial inflammatory effusions that respond to systemic steroids. Enteric pulmonary fistulas have also been reported. Additionally, many of the medications used to treat IBD may also cause lung problems.[2]

Our patient also had the unexpected finding of pulmonary thrombosis on surgical biopsy. Due to the chronic inflammatory nature IBD, it is known to be associated with an increased risk of thromboembolic disease.[2] In patients with overt thromboembolic disease found in CTA chest, VQ scan or Doppler ultrasound, systemic anticoagulation is the standard therapy though the individual risk of intestinal bleeding must be taken into account. Our patient had in situ thrombosis seen only on surgical biopsy with negative CTA chest, VQ scan, and Doppler ultrasound. There are no guidelines to direct therapy of in situ pulmonary thrombosis without other evidence of VTE. In our case, correction of the hypoxic low flow state caused by constrictive bronchiolitis resulted in improvement to diffusing capacity and symptoms without need for anticoagulation.

Conclusion

Awareness and recognition of the pulmonary manifestations of inflammatory bowel disease, particularly ulcerative colitis, can greatly affect patient management. In recognizing this disease process in our patient, we optimized her immunosuppressive and pulmonary therapies with improvement to both bowel and respiratory symptoms.

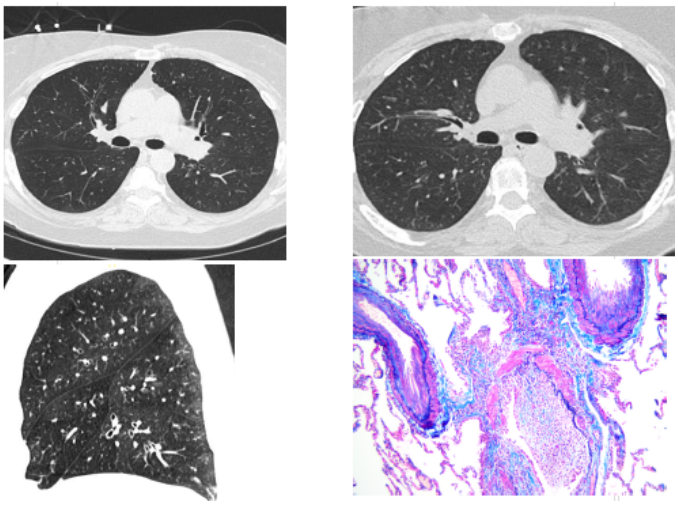
Table and Figures

Table 1. Treatment and PFT response.

Date	UC Therapy	Pulmonary Therapy	FVC	FEV1	FEV1/ FVC	DLCO
June 2017	Infliximab, 6MP, prednisone 7 mg/d	FTC+SML 500/50 mcg BID, TIO 18 mcg/d, MK 10 mg/d, AZM 250 mg TIW	2.21 (70%)	1.10 (45%)	50%	17.24 (78%)
March 2017	Infliximab, 6MP 50 mg/d, prednisone 10 mg/d	FTC+SML 500/50 mcg BID, TIO 18 mcg/d, MK 10 mg/d, AZM 250 mg TIW	2.08 (65%)	0.98 (40%)	48%	17.12 (77%)
June 2016	Infliximab, 6MP 50 mg/d, prednisone 7.5 mg/d	FTC+SML 500/50 mcg BID, TIO 18 mcg/d, AZM 250 mg TIW	1.69 (59%)	0.77 (33%)	55%	15.24 (81%)
February 2016	Infliximab, 6MP 50 mg/d, prednisone 10 mg/d	FTC+SML 500/50 mcg BID, TIO 18 mcg/d, AZM 250 mg TIW	2.07 (72%)	0.99 (42%)	58%	17.02 (90%)
September 2015	Adalimumab, prednisone 20 mg/d	FTC+SML 500/50 mcg BID, TIO 18 mcg/d, AZM 250 mg TIW	2.09 (73%)	0.99 (42%)	58%	14.94 (79%)
February 2015	Adalimumab	BUD+FOR 160/4.5 mcg BID, TIO 18 mcg/d	1.73 (54%)	0.75 (30%)	44%	13.78 (61%)

Key: 6MP = 6-mercaptopurine, TIO = tiotropium inhaler, FTC+SML = fluticasone/salmeterol inhaler, BUD+FOR = budesonide/formoterol inhaler, MK = montelukast, AZM = azithromycin

Figure 1. Representative HRCT chest images demonstrating airway thickening and air trapping. Upper left: inspiratory. Upper right: expiratory. Lower left: expiratory. Lower right: trichrome stain of lung biopsy showing obliterated airways.



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