Respiratory symptoms may develop years after IBD diagnosis
What are the pulmonary manifestations of inflammatory bowel disease? key words: Inflammatory bowel disease, Ulcerative colitis, Crohn disease, Bronchiectasis, BOOP, Interstitial pneumonitis

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abstract: Inflammatory bowel disease (IBD) can have a variety of extraintestinal manifestations, including pulmonary disease. Bronchial involvement is the most common, but other manifestations include upper airway disease; parenchymal involvement, such as bronchiolitis obliterans with organizing pneumonia (BOOP) and interstitial lung disease; and serositis, including pleural effusions and pericarditis. Patients with BOOP may present with fever, dyspnea, cough, and pleuritic chest pain. Chest radiographs show bilateral patchy airspace opacities or a diffuse process; CT scans often demonstrate the opacities to be pleural-based. Corticosteroids appear to be effective in the management of certain pulmonary manifestations of IBD, such as BOOP and pulmonary infiltrates with eosinophilia. (J Respir Dis. 2007;28(6):227-234)

Inflammatory bowel diseases (IBDs), such as ulcerative colitis and Crohn disease, are associated with various extraintestinal manifestations, including articular (peripheral and axial arthropathy), dermatological (pyoderma gangrenosum, erythema nodosum), ophthalmological (episcleritis, anterior uveitis), hepatic (pericholangitis, fatty liver), and other systemic complications. Kraft and associates, in 1976, first recognized respiratory complications secondary to IBD. Six patients with an established diagnosis of ulcerative colitis or Crohn disease were documented to have chronic purulent sputum production of unknown cause. Since then, a limited number of reports of lung disease in patients with IBD have been published. However, many of the reports focus on complications related to the treatment of IBD, such as alveolitis and pneumonitis associated with the use of sulfasalazine and mesalamine. Respiratory complications have been more commonly described with ulcerative colitis than with Crohn disease. In one study of 33 patients, 27 had ulcerative colitis and 6 had Crohn disease. The patterns of presentation (airway disease, parenchymal disease, and serositis) have somewhat different characteristics in terms of sex preponderance and activity of bowel disease. There is a female preponderance of almost a 2:1 ratio for bronchopulmonary complications overall and a 3 to 4:1 ratio for bronchial complications. In contrast, serositis occurs with roughly equal frequency in men and women. Bronchopulmonary complications follow the onset of IBD in 80% to 85% of patients, precede IBD in 10% to 15%, and develop concomitantly in 5% to 10%. While serositis generally manifests during episodes of active IBD, parenchymal lung disease commonly occurs during quiescence.
of the patients with airway disease have undergone colectomy; in some cases, airway symptoms developed days to weeks after colectomy.

The pathogenesis of the pulmonary parenchymal disease and the serositis is unknown. However, the more common airway inflammatory changes have been thought to represent the same type of inflammatory changes that occur in the bowel.²⁻⁵

**SPECTRUM OF LUNG INVOLVEMENT**

Diverse patterns of presentation of pulmonary involvement (airway disease, parenchymal disease, serositis, and abnormal pulmonary function) are seen in patients with IBD (Tables 1 and 2). Among the 33 new cases reported by Camus and associates² and the additional 98 cases from the literature, 41% of the patients presented with some form of airway inflammation, 27% had lung parenchymal involvement, and 17% had pleural involvement; an additional 15% had myopericarditis.³⁻⁶

About 40% to 50% of patients with IBD evaluated in gastroenterology clinics were reported to have had respiratory symptoms, including wheezing, cough, sputum production, and breathlessness. Depending on the type and severity of symptoms, these patients should be further evaluated with pulmonary function tests, chest radiography, and helical or high-resolution CT (HRCT).

**FUNCTION TESTS**

The pulmonary function abnormalities that have been described in patients with IBD include a reduction in carbon monoxide-diffusing capacity (DICO),¹⁸,¹⁹ elevated functional residual capacity,¹⁰ increased residual volume,¹¹ and increased bronchial hyperresponsiveness to methacholine.²⁰,²¹

Tzanakis and colleagues²² compared pulmonary function test results in 123 patients with IBD (47 with Crohn disease; 85 patients with ulcerative colitis) with those in a control group of patients who had intestinal diseases other than IBD. They found no significant difference in spirometry results between the Crohn disease and ulcerative colitis groups or between the 2 IBD groups and the control group. However, DICO was lower in the patients with IBD than in those in the control group (P < .05), and the reduction in DICO correlated with the degree of disease activity (P = .05). Munck and associates²³ studied 26 children with Crohn disease and colitis who had normal chest radiographic findings and found no significant difference in the lung volumes or expiratory flows during periods of active or quiescent bowel disease. DICO (percent of predicted) was significantly decreased during the active phase of disease compared with disease remission (53% ± 15% vs 81% ± 19% of predicted; P < .001), indicating an early interstitial disease process.

**AIRWAY DISEASE**

Inflammation of the trachea, bronchi, and bronchioles can occur in persons who have IBD, with bronchial involvement being the most common.⁴⁻¹⁹ Bronchial involvement may be manifested as bronchiolitis, unexplained chronic bronchitis, or bronchiectasis. Upper airway involvement

Subglottic stenosis is associated with inflammation, friability, and pseudotumors in the trachea.³⁻⁶ These findings have been identified on bronchoscopy in patients with active IBD or preceding the diagnosis of IBD. The clinical presentation of upper airway disease includes cough, dyspnea, purulent sputum, hoarseness, and stridor requiring intubation.

The lack of circulating anti-neutrophil cytoplasmic antibody (ANCA) positivity differentiates patients with IBD from patients with Wegener granulomatosis, who also can have tracheobronchial disease.³,²⁴ A perinuclear ANCA (pANCA) (myeloperoxidase-negative) pattern is found predominantly in patients with ulcerative colitis. The elevated serum levels of pANCA in patients with ulcerative colitis are likely caused by pANCA production in the colonic mucosa. Elevated pANCA levels are detected in 60% to 80% of adults and about 83% of children with ulcerative colitis, but they are less common in patients with Crohn disease (5% to 30%).

**Lower airway involvement**

• **Bronchiolitis:** Although not definitely established, IBD therapy has been suggested as a possible risk factor for bronchiolitis. Bronchiolitis presents with symptoms of bronchorrhea—mild productive cough and wheezing. Small diffuse irregular opacities may be seen on a chest radiograph and are readily recognized on an HRCT scan, along with a mosaic pattern of decreased attenuation interspersed among normal lung parenchyma.²⁵ Air trapping consistent with small-airway involvement is evident on expiratory CT scans. Pulmonary function tests show significant airflow obstruction and reduced forced vital capacity secondary to air trapping.

The histology of lung tissue in patients with Crohn disease and bronchiolitis shows nonscarring epithelioid granulomas and multinucleated giant cells in the bronchial tissue.²⁵ Some patients with bronchiolitis respond to treatment with systemic corticosteroids; in others, pulmonary function may continue to deteriorate despite treatment.

• **Bronchiectasis:** Mahadeva and colleagues⁷ reported the presence of bronchiectasis on HRCT scans from 13 of 17 patients with IBD. Camus and colleagues³ described 3 cases of bronchiectasis that developed within a few days to a few weeks after colectomy. The average time to onset of bronchial symptoms from the time of IBD diagnosis was 7.4 ± 1.9 years. Most patients presented with
unexplained cough and expectoration of variable quantities of mucopurulent sputum, responded poorly to antibiotics, and had recurrences several times a year.

Figure 1 shows the chest radiograph from a patient with IBD in whom bronchiectasis developed. HRCT findings are shown in Figure 2. The findings of thickened, dilated airways or bronchial walls and branched opacities suggestive of mucoid impaction (“tree in bud”) are seen more often on HRCT scans than the “tram lines” on standard chest radiographs.

Butland and associates described 7 nonsmoking patients who had chronic severe unexplained bronchial suppuration and underlying IBD. In 3 of these patients, bronchiectasis progressed rapidly after proctocolectomy; in 5 patients, ulcerative colitis developed before the lung disease. Bronchiectasis manifested in conjunction with an IBD flare-up in 2 patients, while lung disease followed the onset of colitis in 2 others.

A predominance of neutrophils has been detected in bronchoalveolar lavage (BAL) fluid; this appeared to be greater in patients with bronchiectasis or chronic bronchial suppuration than in patients with bronchitis. Culture of BAL fluid and sputum consistently failed to reveal a significant bacterial pathogen. Also, these patients were found to have antinuclear antibodies, smooth muscle antibodies, and elevated serum levels of at least 1 immunoglobulin (IgG). Inhaled corticosteroids were not effective in patients with bronchiectasis; therapeutic success was obtained with long-term oral corticosteroid treatment, although the benefit was often inconsistent or transient.

• **Chronic bronchitis:** The development of a chronic productive cough in nonsmoking patients with IBD may suggest an association between chronic bronchitis and IBD. Culture of BAL fluid and sputum consistently failed to reveal a significant bacterial pathogen. Also, these patients were found to have antinuclear antibodies, smooth muscle antibodies, and elevated serum levels of at least 1 immunoglobulin (IgG). Inhaled corticosteroids were not effective in patients with bronchiectasis; therapeutic success was obtained with long-term oral corticosteroid treatment, although the benefit was often inconsistent or transient.

• **Airway hyperresponsiveness:** In patients with IBD, airway hyperresponsiveness has been documented. Louis and associates studied 38 patients with IBD who had normal findings on chest radiographs and no respiratory symptoms and found a higher incidence of bronchial airway hyperresponsiveness to methacholine in these patients than in control patients (45% vs 17%; \( P < .03 \)). No baseline difference in bronchial caliber was noted.

Atopy, demonstrated by a positive skin test, was also more common in patients with IBD (42% vs 21%). When only non-atopic patients were considered, the rates of bronchial hyperresponsiveness were still higher in the patients with IBD than in those in the control group (9/22 vs 1/19; \( P < .02 \)). Increased nonspecific airway hyperresponsiveness is likely another extraintestinal manifestation of IBD, which in part may be associated with increased airway inflammation.

### Parenchymal disease

Several patterns of lung parenchymal involvement have been described in IBD, with BOOP and interstitial lung disease being the most common. One study of 85 patients with ulcerative colitis and 47 patients with Crohn disease found that DlCO was significantly lower during exacerbations of IBD; however, these transient physiological derangements were unaccompanied by symptoms.

These results suggest that pulmonary inflammation is commonly associated with bowel inflammation.

**BOOP**

This disease presents in an acute or subacute fashion with variable combinations of fever, dyspnea, cough, and pleuritic chest pain. BOOP has been reported to occur 2 months to 36 years after the diagnosis of IBD. The chest radiographic findings are bilateral patchy airspace opacities or a diffuse process, while CT scanning often shows the opacities to be pleural-based and sometimes associated with air bronchograms (Figure 3). A restrictive pattern on pulmonary function studies is seen with BOOP. Treatment with oral or intravenous corticosteroids early in the disease process hastens resolution of symptoms.

**Pulmonary infiltrates with eosinophilia (PIE syndrome)**

Pulmonary infiltrates with eosinophilia has been documented in patients with IBD either as an extraintestinal manifestation or as a complication of sulfasalazine treatment. The reported symptoms were wheezing, chest tightness, slight to moderate fever, night sweats, and malaise. Eosinophilia may be present in both peripheral blood and BAL fluid. The chest radiograph reveals bilateral subpleural peripheral infiltrates consistent with chronic eosinophilic pneumonia. Oral corticosteroid treatment causes prompt and sustained resolution of both the clinical and radiographic abnormalities.

**Necrobiotic nodules**

These nodules are well known to occur in patients with inactive ulcerative colitis. The nodules were associated with constitutional symptoms and high fever resistant to multiple courses of antibiotic therapy. The radiographic appearance of these cavitating nodules resembled Wegener granulomatosis or pulmonary emboli.

Although the nodules have the histological appearance of infectious or noninfectious granulomas, the absence of giant cells and vasculitis or capillaritis are distinguishing features. Furthermore, nonnecrotizing granulomas have not been found in the adjacent parenchymal lung tissue. This histological pattern appears to mimic that of pyoderma gangrenosum skin lesions, an extraintestinal manifestation of IBD. Treatment consists of systemic corticosteroids or cyclophosphamide.
Interstitial pneumonitis
This disease has been reported in patients with IBD. Patients with interstitial pneumonitis usually present with nonspecific findings, such as progressive dyspnea and crackles on chest auscultation. The radiographic features are predominantly bi-basilar interstitial opacities (Figure 4). Pulmonary function tests show a restrictive process and reduced DlCO. Therapy with inhaled corticosteroids has not significantly altered lung function; however, the addition of oral corticosteroids occasionally produces marked improvement in lung function.3

According to one report of a patient presenting with atypical erythema nodosum and arthritis, examination of BAL fluid revealed lymphocytic alveolitis with an elevated CD4:CD8 ratio; Crohn disease was subsequently diagnosed.21 Before the development of perianal abscess and fistula, the most likely diagnosis in this patient was considered to be sarcoidosis. A predominance of lymphocytes in BAL fluid samples has been exhibited in patients with Crohn disease, with no evidence of clinical pulmonary disease.9,27 Lymphocytosis within the alveolar structures is of unknown significance; however, lymphocytic alveolitis (T lymphocytes) is characteristic of all granulomatous lung diseases, including sarcoidosis, hypersensitivity pneumonitis, and berylliosis. Both granulomatous and nongranulomatous interstitial lung disease have been described in patients with Crohn disease and ulcerative colitis.5,28 Sarcoidosis and Crohn disease have several common features: unknown etiology, presence of noncaseating granulomas, erythema nodosum, scleritis, uveitis, accumulation of CD4+ T lymphocytes, and response to corticosteroids. However, these 2 entities can be easily differentiated by the topography of lesions. Sarcoidosis affects the mediastinal lymph nodes, while Crohn disease predominantly involves the digestive system. Nevertheless, the coexistence of sarcoidosis and ulcerative colitis has been reported.29,30

Drug-induced hypersensitivity pneumonitis is a rare but potentially serious complication of therapy with methotrexate and 6-mercaptopurine. A novel treatment that involves monoclonal antibodies directed against tumor necrosis factor a has emerged as a major advance in the treatment of immune-mediated diseases and Crohn disease. Infliximab, which modulates the inflammatory processes in many diseases, is such an agent. However, infliximab is associated with the risk of tuberculosis reactivation in patients with latent disease.32 Although the long-term data on adverse effects are limited, acute respiratory distress syndrome and acute eosinophilic pneumonia have been attributed to infliximab.33

PLEURAL INVOLVEMENT
Serositis, including pleural effusions, pericarditis, pleuropenicarditis, and myopericarditis, has also been recognized as an extraintestinal manifestation of IBD.1,3 Rosenbaum and associates16 described 2 cases of pleurisy in association with ulcerative colitis, in the absence of pleuropenicarditis. In one case, pleuritis occurred during increased activity of the bowel disease; in the other case, pleuritis developed when bowel disease was quiescent. Although these cases of pleuritis could have been independent of the ulcerative colitis, the temporal relationship and absence of another cause after extensive workup suggest that pleuritis may well be a systemic complication of ulcerative colitis.

TREATMENT OF LUNG DISEASE IN IBD
Drug-induced lung disease and superimposed bacterial infection should be considered in patients with IBD who have lung involvement. Whenever drug toxicity is suspected, the alleged offending drug should be withdrawn. In patients with signs of airway disease and chronic purulent sputum production, superimposed bacterial infection must be ruled out. The risk of venous thromboembolism (VTE) is about 3 times higher in patients with IBD than it is in the general population; thus, prophylaxis against VTE should be considered in hospitalized patients with IBD who do not have contraindications to anticoagulation.34,35 The development of unexplained pulmonary symptoms, tachycardia, lower extremity swelling, and/or hypoxemia suggests pulmonary embolism.36
The upper airway lesions may be treated with laser ablation of the inflammatory tissue or intravenous methylprednisolone, followed by oral prednisone, which leads to rapid resolution of most symptoms. In most cases, the tracheal mucosa returns to normal macroscopic appearance with appropriate treatment, and there is no clinical recurrence. However, persistent tracheal and bronchial deformity can occur despite the resolution of the inflammatory process following corticosteroid treatment.23

The only treatment reported to be effective against IBD-related lung disease is inhaled or systemic corticosteroids. Inhaled corticosteroids have been particularly effective in the treatment of large-airway disease, while oral corticosteroids have been used to treat patients with bronchiectasis and excessive sputum production unresponsive to inhaled agents. The dosage of systemic corticosteroids and duration of their use are not well established, although prednisone is often given at a dosage of 0.5 to 1.0 mg/kg for several months.3

A trial of azathioprine and cyclophosphamide was attempted in one patient with bronchiectasis, with no significant improvement in symptoms. In 2 patients, therapeutic BAL was performed, using 0.9% saline and 40 mg of methylprednisolone with or without an aminoglycoside (netilmicin).6 A definitive decrease in bronchial inflammation and a reduction in the amount of sputum production were evident; these patients were subsequently treated with inhaled corticosteroids with variable success. In cases of serositis, a trial of NSAIDs may be attempted, and corticosteroids may be used as a second-line treatment. There is one published report of limited success with corticosteroid-sparing agents (azathioprine or cyclophosphamide).2 Since most of the pulmonary manifestations of IBD appear to be secondary to an autoimmune inflammatory process, the effectiveness of immunosuppressive therapy should be explored in these patients. All of the treatment modalities described above are based on anecdotal experience, since random-ized, double-blind, placebo-controlled clinical trials of corticosteroids (inhaled, oral, or intravenous), NSAIDs, or corticosteroid-sparing agents have not been conducted.

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