Pulmonary involvement of inflammatory bowel disease

Ayse Baha
I. Kivilcim Oguzulgen

Gazi University School of Medicine, Department of Pulmonary Diseases, Ankara, Turkey

Address for correspondence:
I. Kivilcim Oguzulgen, MD
Gazi University School of Medicine
Department of Pulmonary Diseases
Besevler, Ankara, Turkey
Phone: +90 312 2026119 - Fax: +90 312 2129019
E-mail: ikoguzulgen@gmail.com

Summary

Inflammatory bowel diseases (IBD) are chronic inflammatory diseases of the gastrointestinal tract with unknown etiology. Commonality between the gastrointestinal (GI) and respiratory systems provides developmental and pathophysiologic basis for respiratory involvement in IBD. Almost all the pulmonary and airways tissues may be involved, but histology often is not specific of IBD. Pulmonary involvement may be present up to about half of the patients with IBD and it is independent from the duration and activity of disease. Nevertheless, pulmonary involvement in inflammatory bowel disease is generally responsive to steroid treatment. Early diagnosis and treatment is essential in order to prevent the development of persistent pulmonary disease. In this article, we briefly describe the pulmonary involvement during IBD.

KEY WORDS: inflammatory bowel disease, ulcerative colitis, Crohn’s disease, lung granuloma, airway disease, interstitial lung disease.

Introduction

Inflammatory bowel diseases (IBD) are chronic inflammatory diseases of unknown etiology primarily involving the gastrointestinal tract, mainly the colon. Crohn’s disease (CD) and ulcerative colitis (UC) are the two main forms of chronic IBD (1). The occurrence of extraintestinal manifestations (EIM) of IBD has been reported to range from 21 to 41% (2). It has been reported that patients with CD may show extraintestinal manifestations during their life in at least 25% of cases (3). These extraintestinal manifestations may involve skin (erythema nodosum, pyoderma gangrenosum), eyes (uveitis, episcleritis), liver (pericholangitis, hepatosteatosis), joints (peripheral and axial arthropathies) and lungs (4). Lung involvement in IBD was firstly reported in 1976 (5). Commonality between the gastrointestinal (GI) and respiratory systems provides some pathophysiologic basis for respiratory involvement in IBD. Either colon and lung epithelia share embryonic origin from the primitive foregut. Both tissues have goblet cells and submucosal glands as part of their luminal structure. In addition, both lung and GI tract have submucosal lymphoid tissue and play critical roles in host mucosal defense. The aberrations of either innate and acquired immunity may play a pathogenetic role in IBD, but the mechanisms are complex and not yet completely understood (6).

Lung diseases associated to IBD can be classified into six subtypes according to clinicopathological features: airway disease, parenchymal disease, drug induced lung disease, pulmonary vascular disease, serositis or pleural disease (Table 1).

Airway disease

Upper Airway Obstruction

Common forms of airway involvement of IBD are glottic or subglottic stenosis and especially tracheal obstruction due to granuloma formation, especially in patients with CD. These patients usually present with stridor and dyspnea. Histologic features are not specific, so other causes of subglottic stenosis such as intubation, tuberculosis, sarcoidosis and amyloidosis should be excluded (7). Steroid treatment is often effective. Camus et al. (8), found 3 out of 33 patients with IBD having upper airway obstruction, 2 of them had a previous diagnosis of IBD, whilst the other one was recognized having IBD 1 month later the occurrence of airways involvement. These 3 patients nearly fully recovered with both inhaled and systemic steroid treatment (8). A recently reported case of ulcerative colitis and tracheal stenosis requiring tracheostomy, showed a similar inflammatory pattern of either tracheal and colon involvement (9).
Large Airways Disease

Large airways involvement in IBD mainly presents as bronchiectasis and chronic bronchitis. Expectoration of abundant purulent sputum may occur in these patients. Sometimes, the bronchial involvement is localized and involved only few bronchial branches (Figure 1). Pulmonary function tests may show an obstructive defect with decreased FEV1/FVC ratio. Bronchoscopy reveals erythematous mucosal edema and inflammation. As shown in gut biopsy specimens, bronchial biopsy specimens show submucosal lymphocyte, plasmacyte infiltration and mucosal squamous metaplasia and neutrophil infiltration (11). Black et al. (11), reported 171 respiratory pathologies in 155 patients, being the “large airways” the most common site of involvement in IBD, accounting for 39% of all cases, and bronchiectasis was present in 66% of these cases. The second most frequently reported respiratory disease in IBD patients is chronic bronchitis, detected in a surprisingly high proportion (81%) of nonsmoker patients (11). These results confirm the previous findings of Camus et al. where 15 of 33 patients (45.4%) with IBD had large airways involvement, where 6 of them (40%) had bronchiectasis (8). It has been shown that exacerbation of bronchiectasis and intestinal disease occur at the same time (8, 10, 12, 13). In 2010, Yilmaz et al. found 2 bronchiectasis cases among 39 patients with IBD whereas, Ozyilmaz et al. found that among 25 patients with IBD prevalence of bronchiectasis was 66% (14, 15). Interestingly, a case of bronchiectasis associated with mesalazine use was also reported (16). The mechanism of pulmonary toxicity of mesalazine is unknown but an immune-mediated alveolitis is one possibility (17).

Small Airways Disease

Clinically, small airways are rarely affected in IBD. However, high resolution computed tomography (HRCT) has increased the detection rate of small airway involvement in these patients (18). Pathologically, bronchiolitis is the most commonly reported disease involving the small airways in patients with IBD, and it is frequently associated with peribronchial granuloma formation (8, 19, 20). Both Vandenplas et al. and Trow et al. reported granulomatous bronchiolitis in women with CD who had undergone bowel resection (22). Less frequently reported findings include peribronchial inflammation with either neutrophils or lymphocytes and plasma cells, concentric small airway fibrosis, and diffuse panbronchiolitis (11). It has been reported that young people affected by CD may have bronchial hyperreactivity and asthma respectively up to 71% and 17% of cases (23). Kullman et al. showed that metacholine test was positive in 18% of patients with Crohn’s disease and in 8% of patients with ulcerative colitis patients, respectively (24).

Parenchymal diseases

Diffuse Interstitial Lung Disease

Different diffuse parenchymal lung diseases may be variously associated with IBD. According to the review of Black et al., 40 out of 155 patients with IBD had pulmonary parenchymal involvement. Among these patients, 21 had OP, 6 pulmonary nodule, 6 fibrosing interstitial lung disease, 3 pulmonary interstitial emphysema, 1 desquamative interstitial pneumonia (DIP), 1 nonspecific interstitial pneumonia (NSIP), 1 fibroserosis alveolitis/UIP pattern and 1 had eosinophilic pneumonitis (11). Yilmaz et al. showed that among 33 patients with IBD, HRCT revealed reticulonodular pattern in 1 and ground-glass opacity in 8 patients.
Sulfasalazine is responsible for 71% of drug induced diseases (31).

Drug induced diseases

Sulfasalazine (a combination of 5-ASA and sulfapyridine linked through a diazo bond) and mesalamine (5-ASA) have long been used as maintenance therapy in IBD. The most common disease entity associated with these drugs is eosinophilic pneumonia (9-16), which is defined as an infiltration of the lungs with eosinophils, with or without excessive eosinophils in the peripheral blood. The differential diagnosis of pulmonary eosinophilia includes asthma, infection, sarcoidosis, malignancy, and collagen vascular diseases (31). Sulfasalazine is responsible for 71% of drug induced pulmonary pathologies, whereas mesalazine is responsible for the rest 29%.

Up to 40% of these patients have peripheral eosinophilia and 27% has pulmonary fibrosis. Upon drug withdrawal, pulmonary disease resolves within days to weeks. Steroid therapy accelerates recovery time (32, 33). Methotrexate which has recently been shown to be effective when used for long-term maintenance therapy in CD, is associated with a drug induced pneumonitis that can become life threatening (31). Anti-TNF agents are among treatment options for IBD. Recently, increasing number of tuberculosis and pulmonary sarcoidosis cases associated with these agents have been reported. Attention should be paid for secondary infections because of immunosuppression associated with these agents (7).

Overlap Syndrome

Sarcoidosis and CD are both granulomatous diseases, of the lung and bowel respectively, with unknown etiology. Interestingly some cases of IBD and concomitant sarcoidosis have been reported. Genetically, both
CD and sarcoidosis seem to have a genetic component as they are more common in monozygotic than in dizygotic twins. Recently, it has been suggested that CD may be linked to genetic regions on chromosome 12 and 16 (31). Crohn disease and sarcoidosis may also involve eyes, joints and skin apart from intestinal and pulmonary manifestations (37).

Storch et al. (31) documented 46 cases of IBD and concomitant sarcoidosis in a review of the literature in 2003. Black et al. also documented 7 cases of IBD and concomitant sarcoidosis in a review of the literature in 2007 (11). According to our literature search (2007 and onwards), 5 new pulmonary and extra-pulmonary sarcoidosis cases had been reported. 3 of these cases were skin sarcoidosis that developed during anti-TNF treatment. Two of these 3 patients had CD and the other had UC. Other two patients were diagnosed with systemic sarcoidosis during routine follow-up (38-43).

We have identified 7 more reports about this association, bringing the total reported cases of coexisting disease to 58.

α1 antitrypsin deficiency and IBD may be associated, and at least thirteen patients with α1 antitrypsin deficiency and IBD have been reported in the literature (44-47).

**Bronchial fistula (anatomical disease)**

Fistula formation is frequent in Crohn’s disease and occurs in approximately 33% of patients (48). On the other hand, fistulous communication between the pleural cavity and adjacent organs below the diaphragm is an extremely rare complication of Crohn’s disease. The pathophysiology of fistulous tract development in Crohn’s disease is yet unknown (49). Colobronchial fistulas have been quite frequently described in Crohn’s disease and other extraintestinal manifestations (37).

**Why it is important to detect pulmonary involvement?**

A number of reports indicated that the respiratory system is involved more frequently than expected in IBD. Pulmonary involvement is present in about half of the patients with IBD and it is independent from the duration and activity of disease (15). Interstitial pulmonary disease, necrobiosis nodules and serositis respond well to steroid treatment. It is possible to prevent development of persistent airway and parenchymal injuries by early detection of pulmonary involvement. Evidence exists regarding usefulness of exhaled nitric oxide (FE(NO)) to show activity of pulmonary involvement in IBD patients. In a study including 25 IBD patients, Ozylimaz et al. showed that in patients with active pulmonary involvement higher FE(NO) levels were found when compared to controls (15). However, further studies are warranted regarding FE(NO).

**Conclusion**

In light of above-mentioned data, pulmonary involvement secondary to IBD is substantially relevant. Bronchiectasis is the most common form of respiratory tract abnormality seen among patients with IBD, but the spectrum of involvement spans the entire respiratory system, from larynx to pleura. Early diagnosis and treatment is essential in order to prevent development of persistent pulmonary disease.

**References**

A. Baha et al.

45. Lewis M, Kallenbach J, Zaltzman M, Levy H, Lurie D,