Pulmonary manifestations of inflammatory bowel disease: Case presentations and review

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Abstract

Inflammatory bowel disease (IBD) is associated with a number of extraintestinal manifestations that may involve most organ systems. Extraintestinal manifestations are more common in Crohn disease (CD) and may include rheumatologic, ocular, dermatologic, biliary and pulmonary manifestations. The most common pulmonary manifestations of IBD are drug-induced lung disease. Other manifestations include parenchymal disease, pleuritis and overlap syndromes. We present a case series of 7 patients with non-infectious pulmonary manifestations of IBD, which included cryptogenic organizing pneumonia, usual interstitial pneumonitis (UIP), Langerhan’s granulomatosis, and eosinophilic pneumonia. Concurrent extraintestinal manifestations present in these patients included arthralgia, iritis, and pyoderma gangrenosum. In most patients the development of pulmonary disease parallels that of the intestinal disease activity, extraintestinal manifestations and concurrent use of 5-ASA medications.

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1. Introduction

Inflammatory bowel disease (IBD) may be associated with a number of extraintestinal manifestations such as peripheral arthritis, axial arthropathies, ocular and dermatologic complications among others. Extraintestinal manifestations occur in 21 to 41% of patients with IBD, increase with duration of intestinal disease, and are more common in Crohn’s disease (CD) than in ulcerative colitis (UC). First reported in 1976, in six patients with IBD with unexplained bronchopulmonary disease, pulmonary involvement has been recognized with increasing frequency with over 400 cases reported in the literature. Although this phenomenon has been well described in the literature, the pathophysiology, evaluation, and treatment of pulmonary disease associated with IBD remains unclear. Pulmonary manifestations of IBD are commonly associated with concurrent use of drugs typically used to treat the disease. Although this relationship has been described in the literature, it remains difficult to determine whether pulmonary disease is secondary to the...
drugs or to the underlying disease process. Herein we describe a number of diverse pulmonary diseases in patients with IBD and discuss the evaluation and treatment of pulmonary disease in these different clinical scenarios.

2. Case presentations

2.1. Case 1

A 46-year-old male non-smoker with a 27 year history of CD and ileo-colic and several small bowel resections developed high-grade fever (103 °F) and sinus drainage. Medication history included five infliximab (Remicade®, Centocor, Melvin, PA) infusions, most recently two months prior to presentation, azathioprine, 6-thioguanine (6-TG), and multiple courses of steroids. A colonoscopy 1 week prior to presentation revealed a 1.5 cm clean-based ulcer just proximal to the ileo-colonic anastomosis and biopsies were negative for CMV.

A sinus series was normal and the patient was prescribed a 5-day course of azithromycin. Medications included 4.8 g mesalamine (Asacol®, Proctor & Gamble, Mason, OH, U.S.A.) and 25 mg prednisone daily. 6-TG was discontinued one week prior to admission. He continued to have high-grade fevers and mild non-productive cough and was hospitalized. Intravenous cefotaxime and azithromycin were started empirically. Subsequent computed tomography (CT) of the sinuses was unremarkable. A CXR showed possible perihilar infiltrates that were confirmed with high-resolution chest CT (HRCT; Fig. 1). Bronchoscopy with transbronchial biopsy revealed a mixed interstitial infiltrate of neutrophils and small, intermediate, and large lymphocytes. Gram stains, cultures and special stains for infectious etiologies were unremarkable.

Treatment with Solu-Medrol 30 mg IV daily was initiated and mesalamine was discontinued. The patient became afebrile over the last 24 h of hospitalization and discharged in stable condition. Follow-up HRCT two months later showed interval resolution of the bilateral pulmonary infiltrates.

2.2. Case 2

A 56-year-old male former smoker with a 4-year history of CD presented with a two month history of low grade fevers, sinus headaches, progressive cough, and increasing shortness of breath. The patient had a history of arthralgias and iritis well controlled with sulfasalazine and 3 mg of prednisone daily. Endoscopy two months prior to presentation showed very early distal esophageal varices, mild gastritis, and mild patchy colitis. A bronchoscopy was unremarkable, but thoracoscopy demonstrated a diffusely abnormal right lung. Biopsies revealed a pattern of usual interstitial pneumonitis (UIP) with poorly formed granuloma (Fig. 2). No microorganisms were identified on stains and cultures.

The patient was discharged without sulfasalazine and received a two month course of prednisone with minimal improvement in his symptoms. Oral cyclophosphamide 150 mg daily was initiated. After six months of concurrent oral steroid and cyclophosphamide, the patient developed mycobacterium avium complex (MAC) bronchopneumonia. After treatment for MAC was completed, monthly intravenous cyclophosphamide was administered for nine months and dapsone was started for prophylaxis. Mycophenolate mofetil 150 mg oral twice daily was started after the cyclophosphamide course was completed. The patient is currently doing well with stable pulmonary function tests on a regimen of mycophenolate mofetil and low-dose prednisone.

2.3. Case 3

A 20-year-old male non-smoker was recently diagnosed with CD involving the left colon and rectum. Ten to 14 days after mesalamine (Asacol®) was initiated, the patient presented with nausea, vomiting, fever and dehydration. CT scan of the abdomen was unremarkable. However, incidentally the thoracic images revealed bilateral pulmonary base nodules. A subsequent chest CT confirmed scattered ill-defined sub-centimeter nodules with questionable cavitation in one of the larger nodules (Fig. 3). Bronchoscopy was unremarkable and thoracoscopic showed miliary 3–8 mm nodules. Wedge resection showed nodular areas of organizing pneumonia with ill-formed granulomas with no significant necrosis (Fig. 4). Gram stains, cultures, and skin PPD test were negative. Immunostain for S100 protein showed numerous positive-cells consistent with Langerhan's granulomatosis (eosinophilic granuloma of the lung).

An upper endoscopy which was performed to better define the disease extent showed typical ulcers in the stomach consistent with upper gastrointestinal tract CD. Mesalamine was discontinued and the patient was started on 40 mg of prednisone daily with resolution of pulmonary lesion and disease remission.

2.4. Case 4

A 56-year-old male former smoker presented to our IBD clinic with the development of lung disease in the setting of CD. He
had a long-standing history of CD with an ileo-colic and 2 small bowel resections. He was treated intermittently with 5-ASA products (past) and steroids. Other treatments included azathioprine and several infliximab (Remicade®) infusions which were discontinued one year ago. Serial CT scans of the chest revealed worsening bilateral lung infiltrates and the development of a nodular density in the right mid-lung field. Wedge biopsy showed bronchial granulomatous lung disease as well as a focus of cryptogenic organizing pneumonia (COP), consistent with IBD-associated bronchiolitis (Fig. 5). Pulmonary function studies were compatible with a mild obstructive ventilatory defect with no bronchodilator reversibility and with significant hyperinflation and air-trapping with significant maldistribution of air. Prednisone 50 mg daily was initiated with significant improvement of the patient’s symptoms. Subsequent imaging after steroid therapy (Fig. 6) showed centrilobular nodules with branching linear opacities (tree-in-bud pattern), consistent with bronchiolitis, and improvement of the pulmonary infiltrates.

2.5. Case 5

A 17 year-old non-smoker African-American male with a 1-year history of UC presented with fevers, abdominal pain, and progressive right-sided pleuritic chest pain associated with mild shortness of breath, night sweats and chills. His medication regimen consisted of mesalamine (Pentasa®, Shire US Inc., Wayne, PA, U.S.A.) and prednisone 20 mg daily. WBC was 19,700 cells/μl with 77% neutrophils. A chest radiograph showed multiple bilateral patchy nodular opacities not present 2 weeks earlier. A chest CT confirmed multiple bilateral nodules of varying sizes (Fig. 7). Fiberoptic bronchoscopy was relatively normal. Thoracoscopy revealed a number of visible nodules and a wedge resection of the left lower lobe yielded multifocal areas of acute alveolitis with multiple abscesses filled with necrotic debris and neutrophils. Focal vasculitis was present and thought to be secondary to the inflammatory process. Gram stain and cultures were negative and special stains for fungi and mycobacteria were negative as well. The patient did not receive antibiotics, mesalamine was discontinued, and his prednisone dose was increased to 40 mg daily. Pulmonary symptoms improved after admission. Follow-up chest radiograph and computed tomography one month

Figure 2  Lung biopsy (Case 2) showing the usual interstitial pneumonia (UIP) pattern of fibrosis. (A) Old subpleural fibrosis with smooth muscle hypertrophy and peribronchiolar metaplasia (H&E 100×). (B) Normal alveoli admixed with early fibrotic areas showing fibroblastic foci (H&E 40×). (C) Presence of subpleural cystic spaces and bronchioloectasia corresponding to areas of honeycomb lung seen in the chest computerized tomogram (H&E 40×).

Figure 3  Langerhan’s granulomatosis in a 20-year-old man (Case 3). CT shows scattered sub-centimeter nodules.
later showed improvement in size and number of pulmonary nodules and interim resolution of his pulmonary symptoms.

2.6. Case 6

A 37-year-old Caucasian female former smoker presented with UC exacerbation and pyoderma gangrenosum. She had been treated with mesalamine (Asacol®) for eight months when she was initially diagnosed. During the evaluation for pyoderma gangrenosum a chest radiograph was also found to be abnormal but she denied any cough or dyspnea. She was prescribed an empirical course of antibiotics. A chest CT at our institution showed emphysematous and bronchiectatic changes in the left upper lobe with nodular interstitial infiltrate and a cavitary lesion (Fig. 8). Subsequent fiberoptic

![Figure 4](image1)

**Figure 4**  Lung biopsy (Case 3) showing nodules of Langerhans histiocytosis. (A) A lung nodule at low power (H&E 100×). (B) Histiocytes admixed with variable number of eosinophils in the nodule (H&E 400×).

![Figure 5](image2)

**Figure 5**  Transbronchial biopsy (Case 4) showing focal non-necrotizing granulomas in airways. (A) Focal granulomatous bronchiolitis with partial occlusion of the bronchiolar lumen by the inflammatory process (H&E 20×). (B) Non-necrotizing epithelioid granulomas in the bronchial wall (H&E 200×).
bronchoscopy and thoracoscopy were performed. Biopsies of the left upper lobe near the cavity showed patchy areas of organizing pneumonia with prominent bronchiolitis obliterans involving respiratory and terminal bronchioles. Bronchiectasia and centriacinar emphysema were also present. Gram stains, cultures, and special stains were negative. Prednisone 40 mg po daily was started and discharge medications also included mesalamine (Asacol®) 4.8g po daily, and 6-mercaptopurine (6-MP) 50 mg po daily. The patient remained asymptomatic from a pulmonary standpoint and subsequent chest radiographs 4 months and 2 years after treatment, respectively, showed resolution of the pulmonary infiltrates.

2.7. Case 7

A 19-year-old male non-smoker with a 3-year history of chronically active steroid-dependent UC presented with fever of 103 °F, diffuse abdominal pain, bloody diarrhea, and cough. The cough was present over two months and was non-productive, without any associated dyspnea, wheezing, or chest pain. His medications at the time of admission were mesalamine (Asacol®). A chest radiograph revealed patchy opacities distributed in the bilateral upper lung zones and left mid-lung zone. Chest CT showed peripheral and pleural-based bilateral pulmonary infiltrates more prominent in the upper lobes (Fig. 9). CT-guided fine needle aspiration of a peripheral infiltrate was non-diagnostic. Wedge biopsies of the right upper and lower lobes showed a patchy organizing pneumonia with multiple collections of eosinophils mixed with other inflammatory cells, areas of bronchiolitis obliterans with organizing pneumonia, focal vasculitis, and focal bronchiectasia. All gram stains, special stains, and cultures were negative. These findings were collectively consistent with eosinophilic pneumonia, which was believed to be associated with mesalamine (Asacol®), with a component of COP. Mesalamine (Asacol®) was discontinued and prednisone was initiated, with subsequent resolution of respiratory symptoms and radiographic abnormalities on outpatient follow-up.

3. Discussion

Although extraintestinal manifestations of IBD are relatively frequent, clinically evident pulmonary disease is rare. It can present as upper airway disease, large (e.g. bronchiectasis) or small airway (e.g. bronchiolitis obliterans) involvement or...
parenchymal involvement (e.g. eosinophilic pneumonitis and COP). Less commonly the pulmonary vasculature or the serosa may be involved. The etiopathogenesis of the underlying pulmonary pathology in IBD is poorly understood but it may be related to the underlying inflammatory process or drug use.

3.1. Drug-induced complications

Drug-induced lung disease must be considered in all cases where symptoms suggestive of lung involvement develop in a patient with IBD. Sulfasalazine and mesalamine have most commonly been associated with eosinophilic pneumonia, and with pleural effusions and pulmonary fibrosis. All patients in our case series had a history of 5-aminosalicylic acid (5-ASA) use (Table 1). The range of duration of drug therapy (2 weeks to several years) was similar to previously reported cases.

Definitive diagnosis of drug-induced disease is oftentimes difficult. In many cases of pulmonary disease there was no clear association between the use of sulfasalazine or 5-ASA and disease development or recurrence. Specific pulmonary diseases associated with drug use include mesalamine-induced hypersensitivity and interstitial pneumonitis, and both 5-ASA (mesalamine) and the sulfapyridine component of sulfasalazine may cause eosinophilic pneumonia. Further, sulfapyridine and 5-ASA may share a similar moiety that may cause alveolitis. Case 7 presented with eosinophilic pneumonia temporally related to an increase in oral and rectal 5-ASA products, although pulmonary disease regressed with treatment while the patient was continued on mesalamine.

3.2. Airway inflammation

Bronchiectasis, an abnormal and irreversible dilation of medium size bronchioles, followed by chronic bronchitis, are the most common reported diseases of the upper airways in patients with IBD. Patients typically present with cough and variable amounts of sputum production. Chest CT may show dilated airways or bronchial wall thickening as was demonstrated in Case 6. Bronchiolitis, or small airway involvement, has been described in a handful of patients with IBD. Small airway involvement can precipitate abnormalities on pulmonary function tests, as seen in 47 of 82 (57%) cases in a series of patients with IBD and normal chest radiographs. We describe upper airway disease in at least 3 patients (bronchiolitis and bronchiectasis), and 1 case which was complicated by a mild obstructive ventilatory defect on pulmonary function tests.

### Table 1 Clinical characteristics of 7 patients with IBD who developed pulmonary complications.

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender</th>
<th>Age</th>
<th>Disease</th>
<th>Disease duration</th>
<th>Pulmonary disease</th>
<th>Outcome</th>
<th>Acute GI symptoms</th>
<th>Other EIM</th>
<th>Duration ASA</th>
<th>ASA discontinued</th>
<th>Smoker</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>46</td>
<td>CD</td>
<td>27 years</td>
<td>Mixed neutrophilic/lymphocytic infiltrate UIP</td>
<td>Resolved</td>
<td>No</td>
<td>None</td>
<td>Chronic</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>56</td>
<td>CD</td>
<td>4 years</td>
<td>UIP</td>
<td>Stable</td>
<td>N/A</td>
<td>Arthralgias, iritis</td>
<td>Chronic</td>
<td>Yes</td>
<td>Past</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>20</td>
<td>CD</td>
<td>Months</td>
<td>Langerhan’s granulomatosis</td>
<td>Resolved</td>
<td>Yes</td>
<td>None</td>
<td>2 weeks</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>56</td>
<td>CD</td>
<td>30 years</td>
<td>COP Pulmonary Nodules COP</td>
<td>Improved</td>
<td>No</td>
<td>None</td>
<td>Chronic</td>
<td>N/A</td>
<td>Past</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>17</td>
<td>UC</td>
<td>1 year</td>
<td>COP</td>
<td>Resolved</td>
<td>Yes</td>
<td>Pyoderma gangrenosum</td>
<td>8 months</td>
<td>No</td>
<td>Past</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>37</td>
<td>UC</td>
<td>8 months</td>
<td>COP</td>
<td>Resolved</td>
<td>Yes</td>
<td>None</td>
<td>None</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>19</td>
<td>UC</td>
<td>3 years</td>
<td>Eosinophilic Pneumonia/COP</td>
<td>Resolved</td>
<td>Yes</td>
<td>None</td>
<td>3 years</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

M (male); F (female); CD (Crohn disease); UC (ulcerative colitis); EIM (extraintestinal manifestations); ASA (aminosalicylic acid products); UIP (usual interstitial pneumonitis); COP (cryptogenic organizing pneumonia).
3.3. Parenchymal disease

Pulmonary inflammation may correlate with bowel inflammation, as corroborated by studies demonstrating a reduction in diffusing capacity and other pulmonary function abnormalities during IBD exacerbations.\textsuperscript{17,18} Cryptogenic organizing pneumonia (COP), formerly known as bronchiolitis obliterans with organizing pneumonia (BOOP), has been described in about a dozen cases of IBD, more commonly UC,\textsuperscript{19,20} and may present acutely or sub-acutely with fever, cough, dyspnea and pleuritic chest pain.\textsuperscript{15} We presented 3 IBD patients (2 with UC and 1 with CD) with pulmonary features that included COP. Radiographic findings may range from patchy focal opacities to diffuse infiltrates on plain films, to pleural opacities and air bronchograms on chest CT scan. Our cases all showed prominent nodular densities on chest CT. COP has been also associated with autoimmune diseases such as lupus, rheumatoid arthritis, and Wegener granulomatosis.\textsuperscript{9} Interstitial lung disease, i.e. fibrosing alveolitis and eosinophilic pneumonia, has been reported in IBD that was unrelated to sulfasalazine and mesalamine,\textsuperscript{21} although most cases may be drug-induced. We described patients with alveolitis, interstitial pneumonia (UIP), mixed interstitial inflammation, eosinophilic pneumonia, and eosinophilic granulomatosis. Necrobiotic nodules have been described in a few cases\textsuperscript{22} and may also be seen in rheumatoid arthritis, Wegener granulomatosis, or septic pulmonary emboli. The nodules are composed of sterile aggregates of neutrophils with necrosis, a histologic appearance similar to that of pyoderma gangrenosum.\textsuperscript{23}

3.4. Evaluation and management of IBD patients with suspected pulmonary involvement

IBD patients presenting with respiratory symptoms or even asymptomatic pulmonary findings on radiography should be approached with a high index of suspicion for drug-induced or IBD-related pulmonary disease. The history pertinent to IBD should include a careful review of the recent course of the disease, any history of extraintestinal manifestations, and medication use. 5-ASA medications may be resumed with caution, however re-challenge of the possible offending drug for the purpose of diagnosis of drug-induced pulmonary disease is not recommended.

Given these patients are often on immune-modulating drugs and that IBD itself is considered an immune-mediated disease,\textsuperscript{24} infection should initially be ruled out and the evaluation may require screening for tuberculosis or other diseases that IBD patients may be at increased risk for. Radiographic evaluation may begin with standard chest radiographs and should be followed by high-resolution CT in cases with pulmonary disease or high suspicion of pulmonary disease. Characteristic CT findings may be associated with specific diseases (i.e. nodular lesions seen in our 3 patients with COP), as discussed above. Fiberoptic bronchoscopy was commonly utilized for tissue and further infectious disease evaluation, but was usually of low yield. In our observations, thoracoscopy with wedge biopsy is usually required to achieve the final diagnosis (6 of 7 cases).

Although specific management must be tailored to the underlying disease process, general management includes discontinuation of possible offending drugs and initiation of steroids. All patients in our case series on an ASA agent at the time of presentation had this therapy ceased and all patients received steroids (40–50 mg prednisone daily or 30 mg IV methylprednisolone daily) as the first line treatment of their pulmonary disease. Pulmonary disease typically improves with corticosteroids, however—in patients who fail to respond to—second-line therapy should be dictated by the specific disease process and may include immunosuppressives (i.e. cyclophosphamide for steroid-refractory UIP in Case 2). Because pulmonary disease may be asymptomatic and/or associated with continued medication use, serial follow-up imaging after initiation of treatment is recommended for monitoring response to treatment.

4. Conclusion

Pulmonary manifestations of IBD are being increasingly recognized. Invasive measures, such as bronchoscopy and thoracoscopy, are typically required to reach a final diagnosis and treatment is usually initiated with corticosteroids. It is imperative to maintain a high index of suspicion for the development of pulmonary disease in the setting of IBD in order to institute appropriate treatment early and avoid complications.

Conflict of interest

The authors declare that there is no potential conflict of interest related to this article.