PAPER

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Bronchopulmonary manifestations of inflammatory bowel disease: a case report and literature review

[1]GT Ho, [2]JA Innes, [3]AG Shand, [4]J Satsangi

[2]Consultant Respiratory Physician, Department of Respiratory Medicine, [1]Specialist Registrar in Gastroenterology and Internal Medicine, [3]Consultant Gastroenterologist, [4]Professor of Gastroenterology, Department of Gastroenterology, Western General Hospital, Edinburgh, Scotland

ABSTRACT Bronchiolitis obliterans is a rare but well-recognised bronchopulmonary manifestation associated with IBD. This case report is unusual in the severity of the respiratory disease, requiring referral for consideration of lung transplantation with further implications in the clinical management of severe UC. We have reviewed the literature concerning bronchopulmonary manifestations of IBD and discuss the difficulties in distinguishing between a primary manifestation associated with IBD and a side-effect of drug therapy.

KEYWORDS Bronchiolitis obliterans, inflammatory bowel disease, ulcerative colitis

LIST OF ABBREVIATIONS 5-aminosalicylates (5-ASA), angiotensin converting enzyme (ACE), antineutrophil cytoplasmic antibody (ANCA), antinuclear antibody (ANA), bronchiolitis obliterans with organising pneumonia (BOOP), computed tomography (CT), diethylenetriaminepentaacetate acid (DTPA), forced expiratory volume in one second (FEV1), immunoglobulin E (IgE), inflammatory bowel disease (IBD), ulcerative colitis (UC),

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Correspondence to ***GT Ho, Gastrointestinal Unit, Western General Hospital, Edinburgh, EH4 2XU***

tel. ***+44 (0)131 537 1769***

fax. ***+44 (0)131 537 1007***

e-mail ***gwotzerho@aol.com***

CASE REPORT

A 29-year-old Caucasian woman with extensive UC, presented with a relapse of the disease during the third trimester of pregnancy in 1998. Following initial response to oral corticosteroids and the delivery of a healthy female, the clinical course of UC was consistent with corticosteroid dependency with unsuccessful attempts to wean her off this therapy. Further immunosuppressive therapies were discussed, but not used, because she was breast-feeding. Whilst on low-dose corticosteroid and mesalazine (Asacol®) therapy, the patient developed an upper respiratory illness, characterised by a cough, wheeze and breathlessness, two months post-partum. Within four weeks of presentation, her exercise capacity had deteriorated to breathlessness on minimal exertion. On assessment, she was breathless at rest with crepitations audible predominantly over the left lung and clinical evidence of left lower lobe collapse (confirmed by chest X-ray). A computed tomography scan of the thorax demonstrated areas of ground glass opacification within the anterior segments of the right lower lobe and basal segments of the left upper lobe, with total collapse of left lower lobe (see Figure 1). A severe obstructive defect was seen in pulmonary function tests (FEV1 = 0·8 l, Vital capacity = 2·0 l; predicted values of 2·8 l and 3·5 l respectively). Autoantibodies (ANCA, ANA, rheumatoid factor), serum ACE, eosinophil count, total IgE and sputum cultures were within normal limits. An exercise test demonstrated desaturation to 86% on air after two minutes of exercise at 80 watts. Bronchoscopy showed no abnormality in the bronchial tree. A lung biopsy was consistent with bronchiolitis obliterans, demonstrating bronchiolar obliteration associated with poorly formed

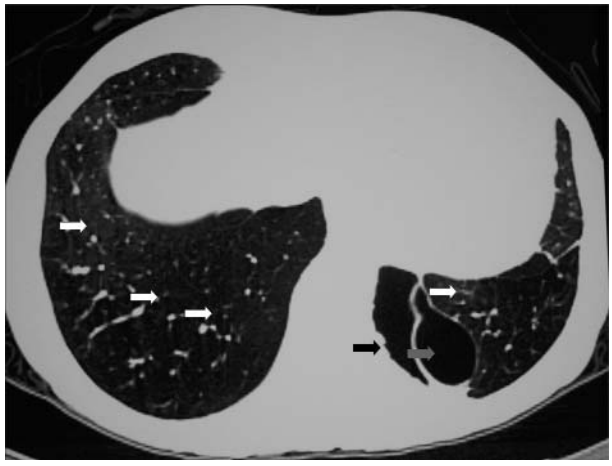

FIGURE 1 Computed tomography-thorax demonstrating bronchiolitis obliterans (white arrows – widespread areas of low attenuation lung parenchyma, peripheral bronchioles and vessels), left lower lobe collapse (black arrow) and adjacent left base cystic bullae (grey arrow).

granulomata with an increase in chronic inflammatory cell infiltrate and connective tissue in the lung interstitium.

Despite high dose corticosteroid therapy and withdrawal of mesalazine, no clinical improvement was evident. The clinical course was critically complicated by two further events; a life-threatening pneumonia requiring ventilation for two weeks, and a further fulminant attack of UC which was unresponsive to prolonged corticosteroid therapy. In view of her poor respiratory function, general anaesthesia for colectomy was not considered safe. Notwithstanding the precarious nature of the illness, remission was achieved after five weeks with triple immunosuppression (cyclosporine, azathioprine and corticosteroids). The severity and irreversibility of her lung disease, and the difficulty in medical treatment of her ulcerative colitis were key factors leading to consideration of lung transplantation in 2000.

Following formal assessment, the decision to transplant was deferred due to an early modest objective improvement in lung function tests, considered to be due either to mesalazine withdrawal or to the profound immunosuppression. At the most recent follow-up (2006), the patient remains significantly breathless on exertion, but has regained an acceptable quality of life. Control of UC is very good. She has had further assessments for lung transplantation but the decision remains deferred.

DISCUSSION

This patient highlighted a rare but well-recognised bronchopulmonary association of IBD, bronchiolitis obliterans. The distinction between a primary manifestation associated with IBD and drug-induced lung disease is difficult, and in this case it remains possible that Asacol® may have played an aetiological role, notwithstanding prior therapy without ill-effects. There is no clear relationship between the development of respiratory symptoms and the institution of therapy.[1–3] In reported cases, the prognosis of mesalazine-induced lung disease in IBD is good, with early response seen on withdrawal of therapy. This was not evident in this case. We present a detailed literature review of reported bronchopulmonary manifestations of IBD, and discuss the possible involvement of mesalazine.

EPIDEMIOLOGY

Bronchopulmonary manifestations of IBD are well described.[3] The exact incidence is unknown, but there have been more than 100 case reports describing lung involvement in association with IBD.[3] There are more case reports associated with UC, suggesting that bronchopulmonary manifestations are more common in UC than in Crohn's disease. Two studies have shown an increased mortality from respiratory diseases including bronchitis, asthma and emphysema in patients with UC.[4, 5] In spite of the well-documented inverse relationship between UC and smoking, the most frequent pattern of respiratory involvement in IBD is airways inflammation. Different forms of interstitial lung diseases may be related to both types of IBD, but, equally, may be induced by treatments such as mesalazine, sulphasalazine and methotrexate.

PATHOPHYSIOLOGY

The pathogenesis of IBD-associated respiratory lesions is unknown. The inflammatory lesions seen beneath the bronchial epithelium are similar to those observed beneath the colonic epithelium in IBD. Both epithelia have columnar structures and mucosal glands, and both sites are challenged constantly by foreign antigens. There are two possible hypotheses:

- A systemic immunologically-mediated phenomenon originating from the intestinal inflammatory process underlies the bronchial/parenchymal changes in the lungs; or
- A defect in the regulation of local immune response which is evident in both gastrointestinal and respiratory tract in response to as yet unknown antigens.

To date, no studies have investigated these hypotheses given the rare occurrence of these manifestations. While clinically apparent bronchopulmonary disease complicating IBD is rare, the function of the small airways and the diffusion capacity of the lungs has been shown to be affected in IBD patients without any clinical respiratory involvement.[6, 7] Heatley *et al.* reported reduced diffusion capacity for carbon monoxide in 25%, and spirometric abnormalities in 50%, of 102 patients with IBD.[8] Adenis *et al.*, using clearance of 99mTechnitium isotopic DTPA, suggested that patients with Crohn's disease may have increased pulmonary vascular permeability due to latent alveolitis.[7]

CLINICAL PATTERNS

Four patterns of respiratory tract involvement are associated with IBD; airways inflammation, interstitial lung disease, necrotic parenchymal nodules, and serositis.[9]

Airways inflammation

The most common pattern is airway inflammation, involving different parts of the bronchial tree from the glottis to the small airways. The inflammatory lesions are similar to those in the digestive tract, and persistent inflammation can lead to airway narrowing and irreversible destruction resulting in subglottic/tracheal stenosis, bronchiectasis and bronchiolitis obliterans.

Bronchiolitis obliterans may be separated pathologically into two subtypes; one with intrabronchiolar plugs of organising connective tissue (proliferative bronchiolitis obliterans), and one in which the bronchiolar walls are inflamed and fibrosed with marked narrowing and complete obliteration of the lumen (constrictive bronchiolitis).[10, 11] Constrictive bronchiolitis obliterans is seen characteristically in connective tissue diseases, IBD, following lung transplantation and, rarely, after bone marrow transplantation.[12–18] Physiologically, this is associated with irreversible airway obstruction and the response to corticosteroids is poor, as evident in this case.

Idiopathic bronchiolitis obliterans is most commonly of the proliferative type, although identical features can be seen after viral infections, toxic fume exposure, systemic diseases and drugs (including sulphasalazine and 5-ASA).[19–21] A restrictive pattern of pulmonary function tests is more typical in this form. Pathological features do not help in determining the aetiology of bronchiolitis, which is established on clinical grounds. However, lung biopsy is helpful in excluding other peripheral lung diseases and in indicating prognosis, since the proliferative type is far more likely to respond to corticosteroids than the constrictive type.

Interstitial lung disease

Interstitial lung diseases are disorders with infiltration of the alveolar air spaces or thickening of pulmonary interstitial structures. The most common pattern associated with IBD is BOOP.[22] This is characterised histologically by proliferative bronchiolitis obliterans with extension of inflammatory changes distally into the alveolar ducts and alveoli. Typically, BOOP associated with IBD responds well to corticosteroid treatment.[3]

Necrotic parenchymal nodules

Necrotic pulmonary parencyhmal nodules occur more commonly in UC.[9] These nodules are sterile neutrophilic aggregates which destroy the lung parenchyma and can lead to lung cavitation. This is can be associated with pyoderma gangrenosum. Histologically, these lesions resemble those of pyoderma gangrenosum of the skin. Symptoms include fever, cough, dyspnoea and chest pain, typically of acute onset. Chest X-rays show multiple nodules, which eventually cavitate. The main differential diagnosis is pyogenic abscesses.

Serositis

Serositis in the form of pleuritis and pericarditis is a well-described rare extra-intestinal manifestation of IBD. It can also be drug-induced by sulphasalazine and 5-ASA. Anti-nuclear antibodies may be present in cases of sulphasalzine-induced lupus.[23, 24] Camus *et al.* reviewed 45 cases of pericarditis with or without pleuritis in the literature.[9] The majority were not drug-related and occurred in patients with active IBD. Response to corticosteroids is usually good, although pericardiocentesis or pleural aspiration may sometimes be necessary.

DRUG-INDUCED BRONCHOPULMONARY DISEASE

Drug-induced interstitial lung disease has been well-reported in IBD, with clinical features very similar to IBD-associated interstitial lung diseases. Most cases have been attributed to salicylates and mesalazine therapy.[25] Salicylates (sulphasalazine and 5-ASA) can induce different lung diseases such as bronchiolitis obliterans, BOOP and interstitial pneumonitis with the most common being eosinophilic pneumonitis. The exact mechanism by which salicylates and mesalazine cause bronchiolitis obliterans and BOOP is unknown. Hypersensitivity pneumonitis was believed initially to be secondary to the sulphapyridine moiety,[26–28] but, increasing reports of pneumonitis have been described in patients on mesalazine therapy.[1, 2, 29, 30] Intriguingly, one case report has described bronchopulmonary disease in a patient receiving rectal mesalazine therapy.[30]

Drug-induced lung disease can be confirmed by drug re-challenge and improvement has occurred following drug withdrawal. Our opinion is that this should be avoided due to an unfavourable risk/benefit ratio (as in this case) and for fear of precipitating further deteoriation in lung function. Generally, prognosis is favourable in the majority of salicylate-induced interstitial lung diseases, but fatal outcomes due to irreversible lung fibrosis and rapidly progressive interstitial lung disease have been described.[9] The distinction between drug-induced interstitial lung disease and that associated with IBD can be very difficult. A high index of suspicion is required in patients developing respiratory symptoms on salicylate or mesalazine therapy. In all cases, the drug must be withdrawn and a trial of corticosteroids given.

Hypersensitivity pneumonitis may occur with methotrexate. This is a serious complication, occasionally fatal, with a reported prevalence of 3·1 to 11·6% in patients receiving long-term low-dose therapy.[31, 32] The clinical features include dyspnoea, fever and cough with diffuse alveolar and interstitial shadowing on chest X-ray. Treatment requires the immediate withdrawal of methotrexate and high dose corticosteroids. A few cases of azathioprine-induced interstitial lung diseases have been reported in non-IBD patients. Opportunistic infections have been described in patients treated with immunosuppressants, particularly cyclosporin, and most recently, infliximab (anti-tumour necrosis factor agent).[33, 34]

CLINICAL PRESENTATION

Respiratory symptoms can occur at any time in the history of IBD. Camus *et al.* studied 33 patients with IBD

and pulmonary disorders,[9] pulmonary manifestations occurred on average nine years after diagnosis and only 11% had active bowel disease at the onset of pulmonary symptoms. Other extra-intestinal involvement was present in two thirds of the patients. Colectomy has appeared as a risk factor for pulmonary disease in several series, with pulmonary symptoms occurring immediately after surgery.[19,35]

Most interstitial lung diseases associated with IBD start gradually with weeks or months of breathlessness associated with cough. Bronchiolitis can progress unrecognised as there is no distinctive pattern of physical signs.[36] Despite exertional dyspnoea, there may be no audible signs on auscultation. Radiological signs are also variable. Chest radiographs may show diffuse or patchy infiltrates but can be normal. Computed tomography scan is more helpful in demonstrating diffuse nodular or ground glass opacities which maybe patchy or uniform.[37] Pulmonary function tests usually show a restrictive defect in interstitial lung involvement with reduced gas transfer and resting/exercise hypoxaemia. Broncho-alveolar lavage, useful in ruling out infectious causes, generally shows lymphocytosis. A lung biopsy is usually necessary to confirm the diagnosis and may aid in indicating prognosis.[3]

MANAGEMENT AND OUTCOMES

Most respiratory disease associated with IBD responds well to corticosteroids with the exception of constrictive bronchiolitis obliterans.[38] It is unknown whether other immunosuppressive treatments such as Azathioprine and 6-Mercaptopurine are effective. Bentur *et al.* reported a 13-year-old Crohn's disease patient with bronchiolitis obliterans and granulomatous lung disease who improved following treatment with 6-mercaptopurine and corticosteroids.[22] Other case reports have recorded beneficial effects from immunosuppressive agents such as methotrexate, cyclosporin and tacrolimus in the treatment of bronchiolitis obliterans in non-IBD conditions.[39–42]

Initial treatment of airways inflammation is with inhaled corticosteroids. Systemic corticosteroids are used to treat parenchymal disease (BOOP, interstitial pneumonitis and necrotic nodules). Methotrexate or salicylates should be withdrawn as potential causes of interstitial lung disease. The duration and dosage of corticosteroid treatment should be guided by symptomatic response and pulmonary function tests. In the case of BOOP, the duration of corticosteroid treatment is usually six months and clinical improvement can be seen within days to weeks.[43] Colonic resection has no effect on the progression of lung disease and may even worsen respiratory disease.[3] In rare cases, lung transplantation may be appropriate although, to our knowledge, this has never been reported.

CONCLUSION

Inflammatory bowel disease-associated and drug-induced respiratory diseases are uncommon but well-recognised particularly in UC. A high index of suspicion is important, as the outcome is usually favourable with early corticosteroid treatment and the removal of offending drugs. In some patients, pathological changes such as bronchiectasis and bronchiolitis obliterans are irreversible.

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