Mesalazine-induced bronchiectasis and eosinophilia in a patient with ulcerative colitis: a case report

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We describe a case of mesalazine-induced eosinophilia and bronchiectasis in a patient with ulcerative colitis, and discuss the diagnostic challenges involved.

CASE REPORT

A 28-year-old female was diagnosed in 1994 with ulcerative colitis extending from rectum to transverse colon. By 1999, this had progressed to a pancolitis, following which her symptoms had been controlled with mesalazine 400 mg t.d.s. (Asacol, Proctor & Gamble Pharmaceuticals). She was referred to the respiratory team in 2004 with an eight-month history of productive cough, wheeze, nasal congestion, nocturnal fevers and weight loss. Chest radiography revealed right basal bronchial wall thickening. High-resolution computed tomography scanning showed central cylindrical bronchiectasis in the right lower and middle lobes, with fine nodular shadowing throughout the lower lobe (Figure 1), in keeping with bronchiectasis and associated mucus plugging.

At presentation, she had a peripheral eosinophilia of $2.0 \times 10^9/L$ (normal range $0.0\text{--}0.5 \times 10^9/L$), normal immunoglobulin E (IgE) levels and erythrocyte sedimentation rate was elevated at 50 mm/hour. Anti-neutrophil cytoplasmic antibodies were negative. Sputum cultured normal flora and was negative for acid-fast bacilli. Initial lung function showed a slight reduction in FEV1, but no evidence of reversibility or airway variability suggestive of asthma. Bronchoscopy revealed inflamed mucosa and purulent secretions throughout the bronchial tree. Right lower lobe broncho-alveolar lavage (BAL) cytology showed 95% neutrophils, scanty alveolar macrophages and bronchial epithelial cells, with no eosinophils.

Figure 1 CT scan showing cylindrical bronchiectasis

The cough and purulent sputum persisted following a week of oral amoxycillin 500 mg t.d.s., then clarithromycin 500 mg b.d. for one week, with low-dose inhaled steroids during this time. Following this, the peripheral eosinophil count remained elevated at $1.6 \times 10^9/L$. With the knowledge that bronchiectasis related to ulcerative colitis itself is well described, is steroid-responsive to an extent^{1,2} and eosinophilia is unusual,² it was hypothesized that mesalazine might be the cause of the eosinophilia and productive cough. Hence, prednisolone 25 mg daily was substituted for the mesalazine both for the respiratory symptoms and for maintenance of ulcerative colitis remission. When reviewed four weeks later she was well and the eosinophil count had normalized.

She remained well until three months later when a flare of ulcerative colitis was diagnosed and she was initiated on azodisalicylate (olsalazine, Dipentum) 500 mg t.d.s. Shortly after this, similar symptoms of cough and sputum production recurred. She stopped the new medication herself, following which these respiratory symptoms resolved almost immediately. It was felt that there was a close temporal link between onset and recovery of the same respiratory symptoms and the challenge of the second 5-ASA agent. Without further similar agents, high-resolution computed tomography at six months showed very mild residual bronchiectatic changes and overall marked improvement, and she remains asymptomatic.

DISCUSSION

There is an association between ulcerative colitis and several pulmonary disorders including large airway stenosis, tracheobronchitis, bronchiectasis, constrictive bronchiolitis,¹ panbronchiolitis, necrobiotic nodules, bullae, bronchiolitis obliterans organizing pneumonia, pulmonary vasculitis, apical fibrosis and rarely, pulmonary infiltrates

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with eosinophilia.^{1,2} Ulcerative colitis-induced bronchiectasis is well described but is rarely associated with eosinophilia.²

Many of the 5-ASA medications prescribed for the treatment of ulcerative colitis are associated with adverse pulmonary reactions. The inflammatory action is thought to include induction of manganese superoxide dismutase, inhibition of nuclear factor kappa B activation and direct antioxidant activity.³

Sulphasalazine consists of the active 5-ASA and sulphapyridine (a sulphonamide) linked by an azo bond. Systemic toxicity is thought related to the sulphapyridine moiety,⁴ resulting in fever, rash, haemolytic anaemia and arthralgia.⁵ Pulmonary manifestations, characterized by cough, dyspnoea and bilateral patchy infiltrates with or without peripheral eosinophilia, are also believed to represent a hypersensitivity reaction to the sulphonamide⁶ and histopathologically include progressive interstitial fibrosis, interstitial pneumonitis⁴ and bronchiolitis obliterans.²

Mesalazine lacks the sulphonamide moiety, thus reducing toxicity and allergic reactions. However, pulmonary abnormalities have been reported, albeit uncommonly, including interstitial infiltrates, consolidation and pleural effusions.

The mechanism of pulmonary toxicity is unknown but an immune-mediated alveolitis is one possibility.³ Overall, mesalazine tends to affect lung parenchyma more than inflammatory bowel disease (IBD) itself, which tends to involve large airway abnormalities.² A review of mesalazine-related pulmonary disorders in patients with IBD³ included four patients with evidence of peripheral eosinophilia⁷ and two with eosinophilia in the BAL fluid, but eosinophilia with bronchiectasis has not been described.

Given the variety of histological patterns seen, there is no specific BAL pattern seen in mesalazine lung disease, nor in fact for any drug-induced lung disease. BAL findings in these cases are most helpful when correlated with the expected clinico-pathological findings, and in the exclusion of differential diagnoses such as infection or malignancy. The neutrophilia in the BAL fluid in this case was likely to be a non-specific finding, although we acknowledge that the presence of BAL eosinophilia would have strengthened the link between drug and bronchial effects further.

We postulate that the bronchiectasis and peripheral eosinophilia were the result of mesalazine use in this patient. The onset of symptoms five years after the introduction of therapy is longer than in previous reports,

although there is a large range in time-course, from five days to 44 months.⁷

Ulcerative colitis-associated bronchiectasis usually improves with steroids,^{1,2} and eosinophilia is unusual, as described. We could not be certain whether it was the introduction of prednisolone or the withdrawal of mesalazine that was responsible for the initial resolution of the peripheral eosinophilia, but the patient was symptomatic and also required treatment for the ulcerative colitis. The later use of olsalazine constituted a 5-ASA 'challenge', however, which reproduced the same respiratory symptoms after a period of remission. This, with the improvement after discontinuation of both agents, was considered evidence for a drug class effect. Re-challenges with different ASA-class drugs have been described previously, sometimes leading to symptom recurrence⁸ but sometimes not.⁹ However, drug re-challenge is not normally carried out, for obvious reasons.

Distinguishing between ulcerative colitis and drug-induced pulmonary complications can be a challenge. Mesalazine is a recognized cause of several pulmonary complications but the combination of eosinophilia and bronchiectasis has not previously been described in a patient with ulcerative colitis.

Competing interests None declared.

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