Mesalazine-induced Bronchiolitis Obliterans Organizing Pneumonia (BOOP) in a Patient with Ulcerative Colitis and Primary Sclerosing Cholangitis

To the Editor:

5-Aminosalicylates are commonly used agents in the management of inflammatory bowel disease (IBD). While they are generally safe and well tolerated, uncommonly they may be associated with significant adverse reactions. Pulmonary side effects of aminosalicylates are rare, while bronchiolitis obliterans organizing pneumonia (BOOP) is exceedingly rare, with only three previous reports to our knowledge.

We report mesalazine-induced BOOP occurring in a 17-year-old man admitted with a 5-week history of cough, dyspnea, and pleuritic chest pain. His background medical history was of primary sclerosing cholangitis with associated portal hypertension and recently diagnosed ulcerative colitis (UC). Four months previously he was begun on mesalazine 2 g twice daily along with an oral corticosteroid (prednisolone 40 mg tapering by 5 mg weekly over 2 months) as therapy for active UC. He had not previously been on an oral 5-aminosalicylate. His other medications at presentation were calcium supplements, ursodeoxycholic acid, omeprazole, and propanolol. On initial evaluation he was normotensive, apyrexial, and tachypnoeic with oxygen saturations of 95% on room air. Initial blood profile revealed a normochromic, normocytic anemia with a hemoglobin of 11.5 g/dL (13–18 gdL); a leukocytosis with a white cell count of 16×10^9/L ($4–11 \times 10^9$/L); and a peripheral eosinophilia 3.74×10^9/L ($0.04–0.4 \times 10^9$/L). C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were also markedly elevated, being 74 mg/L (0–10 mg/L) and 65 mm/hr (1–12 mm/hr), respectively. Arterial blood gas showed mild type 1 respiratory failure with a pO_2 of 10.4 kPA (11.4–14.4 kPA) and pCO_2 4.87 (4.67–6.4 kPA). Chest radiograph revealed air space opacification in the right upper zone and left mid-lower zone in keeping with pneumonic consolidation, with more peripheral opacities in both upper zones noted also. He was treated presumptively for pneumonia with intravenous piperacillin/tazobactam and underwent imaging to rule out a pulmonary embolism. A computed tomography (CT) pulmonary angiogram demonstrated no pulmonary embolism but revealed consolidation in both right upper and lower lobes in a peripheral distribution and the left upper lobe in the peri-hilar region.

Antibiotic therapy was continued over a 72-hour period with no significant improvement, while sputum and blood cultures did not isolate any organism. A high-resolution CT thorax demonstrated multiple patchy areas of consolidation and rounded pleural-based lesions in the lateral aspects of both upper lobes measuring up to 3 cm in diameter. A bronchoscopy was performed which showed no macroscopic abnormality. Bronchoalveolar lavage demonstrated no elevation in the eosinophil count, no organisms, or acid fast bacilli. Based on highly suggestive imaging findings and the recent commencement of mesalazine, a diagnosis of drug-induced BOOP was made.

Following discontinuation of mesalazine and commencement of intravenous hydrocortisone there was a marked symptomatic improvement; therefore, a lung biopsy was not performed. After a week of intravenous steroids, a tapering course of oral steroid was begun and the patient was discharged. Repeat blood profile 6 weeks post discharge showed a normal CRP 4 mg/L and eosinophil count 0.35×10^9/L. Repeat chest radiograph demonstrated complete resolution of previous pulmonary infiltrates. The patient is currently well and 5-aminosalicylates have not been reintroduced.

BOOP is a distinct clinical entity with predominant features of pneumonia, rather than a primary airway disorder. Organizing pneumonia can also be seen in association with connective tissue diseases, a variety of drugs, malignancy, and other interstitial pneumonias.[1,2] BOOP is characterized by a number of histopathological features including excessive proliferation of granulation tissue within small airways (proliferative bronchiolitis) and alveolar ducts with associated chronic inflammation in the surrounding alveoli.[3] This organizing pneumonia is the most important process underlying the clinical and radiographic manifestations of BOOP; however, its pathogenesis remains unclear.

This patient presented with typical symptoms and radiological findings associated with BOOP. The interval of 4 months from commencement of mesalazine to presentation is most likely explained by the initial cotreatment with oral corticosteroid, with BOOP only evolving following withdrawal of oral prednisolone. A diagnosis of BOOP was made on account of the failure of improvement on intravenous antibiotics, lack of evidence of pulmonary sepsis, suggestive imaging findings, and recent commencement of mesalazine. The clinical time course and radiological picture were felt to be most supportive of BOOP rather than eosinophilic pneumonia and eosinophils were not seen on BAL. While the gold standard for the diagnosis of BOOP is a lung biopsy, we elected not to perform this procedure as the imaging findings were so suggestive and

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the patient made a marked improvement following commencement of intravenous corticosteroids and withdrawal of mesalazine.

While drugs are a common cause of BOOP, reports of this entity occurring in association with aminosalicylate use are few. There are two reports of mesalazine-induced BOOP in patients with IBD: the first occurring in a patient with Crohn's disease following 2 months of therapy,[4] the second in a patient with UC.[5] There is a further report of BOOP occurring in a 68-year-old female patient with rheumatoid arthritis treated for 6 months with sulfasalazine.[6]

In summary, this is the third report of mesalazine-induced BOOP occurring in a patient with IBD. While aminosalicylates are generally safe and well tolerated, serious pulmonary side effects occur rarely. BOOP should therefore be considered in patients with unexplained respiratory symptoms who are using aminosalicylates.

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