Organising Pneumonia Secondary to 6-Mercaptopurine in a Patient with Inflammatory Bowel Disease

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Abstract

A 45 year old woman with a background of ulcerative colitis presented with a history of non-productive cough and progressive shortness of breath that failed to respond to antibiotics. She had been commenced on 6-Mercaptopurine (6-MP) for Inflammatory Bowel Disease (IBD) six weeks prior to developing respiratory symptoms. Laboratory and radiological investigations suggested a pneumonic process that failed to resolve following broad-spectrum intravenous antibiotics. A thoracoscopic biopsy demonstrated features consistent with organising pneumonia, which was felt to be secondary to 6-MP as her symptoms coincided following the introduction of the drug. There was complete resolution of pneumonic changes following cessation of 6-MP. This case highlights the importance of considering 6-MP as a potential cause of organising pneumonia in appropriate clinical context.

Keywords: 6-mercaptopurine; Organising pneumonia; Ulcerative colitis

Introduction

Organising pneumonia is characterised by histopathological evidence of intra-alveolar fibroelastic plugs and unil or multi-focal consolidation in a bronchovascular distribution on thoracic imaging. There is no gender predilection and it usually presents in the fifth decade. The most common clinical presentation is of a non-resolving lower respiratory tract infection with symptoms of shortness of breath, non-productive cough and malaise. A careful history is invaluable to determine if the Organising Pneumonia is Cryptogenic (COP) or if it is secondary to infection, medication or associated with another underlying condition such as a connective tissue disease. The aetiology of organising pneumonia is diverse (Table 1) and the key to diagnosis is a thorough clinical history that includes exposure to any potential drugs implicated in the causation of this interstitial lung disease.

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the clinico-radiological picture, coupled with lung biopsy, was consistent with organising pneumonia secondary to 6-MP. With the cessation of 6-MP, the patient made an excellent recovery and radiological abnormality resolved completely 4 months after the initial presentation (Figure 5) and patient is well at 18 months of follow up.

Discussion

Organising pneumonia is a distinct disease entity that usually presents with progressive shortness of breath and should be considered in a patient who fails to respond to antibiotic treatment. It can be divided into three categories dependent on the aetiology [1,2]; organising pneumonia of determined cause, Organising Pneumonia of unknown cause or Cryptogenic (COP) and organising pneumonia of undetermined cause but occurring in a specific clinical context such as granulomatous disease or vasculitis. Our case had a background of inflammatory bowel disease which is well recognised to have an association with a variety of lung pathologies including organising pneumonia. It was felt, however that given the timing of onset of symptoms and the improvement on cessation of the 6-MP that this was the cause of the organising pneumonia.

Organising pneumonia or Bronchiolitis Obliterans Organising Pneumonia (BOOP) was originally described as a failure of

Figure 1: Chest radiograph showing predominantly left sided peripheral consolidation.

Figure 2: A repeat chest radiograph 6 weeks after the initial presentation shows worsening consolidation on left side.

Figure 3: (a) CT thorax at the level of upper lobes demonstrating bilateral consolidation in a perbronchovascular distribution with ground glass change associated with it. This radiological picture is highly suggestive of organising pneumonia. (b) Similar findings to figure 3 (a) but at a lower cross sectional level of thorax.

Figure 4: (a) Video Assisted Thoracoscopic (VATS) lung biopsy showing resolving organising pneumonia. There is evidence of granulation tissue with fibroblastic plugs in the biopsy specimen (arrows). (b) Lung biopsy demonstrating inflammatory cell infiltrate including eosinophils and lymphocytes

Figure 5: Follow up chest radiograph showing complete resolution of parenchymal infiltrates.
resolution of typical acute lobar pneumonia and the pathological hallmark of organising pneumonia i.e., Masson bodies were described by Masson and colleagues in association with rheumatoid arthritis. It is an interstitial lung disease with generally a favourable prognosis and may resolve spontaneously. It is generally recommended to commence corticosteroids in organising pneumonia; particularly when it is idiopathic (COP), however, this recommendation is not supported by high quality randomised clinical trials and is based on observational and retrospective studies [3-6]. The decision to commence corticosteroids in cases of organising pneumonia should be based on individual patient characteristics and a frank discussion with a well-informed patient taking into account the potential adverse effects of high dose corticosteroid use and the clinical benefit likely to be achievable.

Thiopurine analogues such as azathioprine and 6-MP are commonly prescribed in the treatment of Inflammatory Bowel Disease (IBD) as immunomodulating drugs. These drugs are used as maintenance therapy as well as steroid sparing agents in IBD. A variety of different toxic pulmonary patterns secondary to azathioprine have been reported in literature including interstitial pneumonitis [7], pulmonary fibrosis and pulmonary oedema [8]. However, there is paucity of data regarding 6-MP induced pulmonary toxicity. Ananthakrishnan et al., [9] reported 3 cases of severe non-infectious pulmonary toxicity within one month of commencing azathioprine/6-MP for IBD. Histopathological examination revealed BOOP and Usual Interstitial Pneumonia (UIP) and all 3 patients improved after the cessation of therapy. Our patient had slightly delayed symptoms as compared to this case series and one of the patients in this series had similar histological profile as described in our case (i.e., BOOP).

Mechanism of pulmonary toxicity by thiopurines

Although the exact mechanism of 6-MP related pulmonary parenchymal injury is unknown, we believe it is due to immunologically mediated mechanisms from the drug and its metabolites. A variety of mechanisms of pulmonary alveolar injury may be responsible as there are multiple patterns of toxicity seen due to these drugs. In our opinion, the most likely mechanism in 6-MP induced lung injury is combination of alveolitis and pulmonary oedema followed by impaired tissue repair that leads to the formation of granulation and fibrotic tissue. Furthermore, hypersensitivity reaction in the form of pneumonitis accompanies the subsequent changes seen in pulmonary interstitium. The initial inflammation is linked with direct effects of 6-MP to pulmonary tissue and subsequent aberrant repair led to organising pneumonia development that responded to cessation of therapy with thiopurine. It is important to acknowledge that actual frequency of pulmonary toxicity due to 6-MP is unknown and reporting similar cases to ours will highlight the scope of the problem and help elucidate underlying pathogenetic mechanisms involved in the development of pneumonitis and organising pneumonia.

Key Points

This is a rare association between 6-MP and the development of organising pneumonia. Although organising pneumonia is a relatively rare condition it will often present to the general and acute physicians as a non-resolving pneumonia or lower respiratory tract infection. It is important for general, respiratory and acute physicians and gastroenterologists to be aware of the association described. Moreover, this case highlights the importance of thorough clinical history and clinicians having a high index of suspicion to identify potential cases of 6-MP related organising pneumonia and pneumonitis that may have been under-recognised and under reported.

Conflicts of Interests

None to declare for any of the authors in relation to this manuscript

Patient Consent

Obtained

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