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Case report

A case report of mesalazine-induced lung injury: A reversible drug side effect

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ABSTRACT

Introduction: Mesalazine is widely used in the treatment of the acute and maintenance phase of ulcerative colitis (UC). The possibility of interstitial lung disease being induced by mesalazine in the form of eosinophilic pneumonia, organizing pneumonia, and nonspecific interstitial pneumonia has been acknowledged for decades. However, mesalazine-related hypersensitivity pneumonitis (HP) constitutes an infrequent entity.

Case report: A 55-year-old Caucasian man, with a six-month medical history of UC under long-term maintenance treatment with oral mesalazine, presented with a week-long low-grade fever, dry cough and a diffuse bilateral centrilobular ill-defined micronodular pattern in chest imaging. On examination, he had dyspnea with hypoxemic respiratory failure. After extensive workup, potential differential diagnoses such as pulmonary infections were ruled out. Bronchoalveolar lavage (BAL) cellular analysis demonstrated a predominance of lymphocytes and an eosinophilia. The transbronchial biopsy findings confirmed lymphocytic alveolitis. The diagnosis of subacute HP was made with confidence because of the compatible clinical, radiographic, physiologic, BAL and histopathologic findings. Mesalazine withdrawal was decided. Substantial clinical improvement was promptly noticed. The fever abated within 24 hours alongside with a significant improvement of arterial oxygen saturation and lung function parameters. A radiological recovery was also gradually noticed.

Conclusions: Mesalazine-induced HP has been scarcely described in the literature. This Case indicates that HP is a rare but real entity in UC patients on continuous oral mesalazine treatment; its possibility should also be considered when unexplained respiratory symptoms develop during therapy. Amelioration of symptoms, imaging, and lung function improvement seem to occur only upon the abrupt drug discontinuation.

1. Introduction

Amino-salicylates (5-A-SA) such as sulfasalazine and mesalazine are commonly prescribed medications for the long-term treatment of inflammatory bowel disease. Regarding ulcerative colitis (UC), they are useful in the treatment of active disease as well as in preventing relapses of the disease in remission [1]. Numerous Case reports have been published implicating sulphasalazine in pulmonary toxicity. On the other hand, mesalazine is an anti-inflammatory agent that does not contain the sulfa moiety, the incriminating agent which is associated with pulmonary side-effects. The mesalazine-induced lung injury presented with various patterns of interstitial lung disease has been reported in the literature as a rare entity with fewer than 50 published reports in the English literature. However, the incidence of mesalazine-related lung reaction is unknown. According to the European Crohn and Colitis Organization Guidelines latent interstitial pulmonary involvement complicates about 20%–55% of patients with inflammatory bowel disease and the most common pulmonary manifestation of IBD is drug-induced lung disease which is mainly attributed to 5-ASA or methotrexate [2]. Here we present a case study with a recent diagnosis of UC in remission, treated with oral mesalazine, who developed an ill-defined micronodular pulmonary pattern as an adverse drug reaction. Diagnostic workup attributed exclusion to other common causes. The evaluation of transbronchial biopsy and bronchoalveolar lavage (BAL) fluid cytology, as well as the impressive clinical improvement after drug discontinuation, led to the final diagnosis of mesalazine-induced hypersensitivity pneumonitis (HP).

2. Case presentation

A 55-year-old Caucasian man, with a smoking history of about 40 pack years, being diagnosed with UC four months ago, presented to the

Abbreviations: BAL, Bronchoalveolar lavage; FEV_1, Forced expiratory volume-one second; HRCT, High-resolution computed tomography; HP, Hypersensitivity pneumonitis; PaO_2, Partial pressure of oxygen; $PaCO_2$, Partial pressure of carbon dioxide; RT-PCR, Reverse transcriptase polymerase chain reaction; UC, Ulcerative colitis

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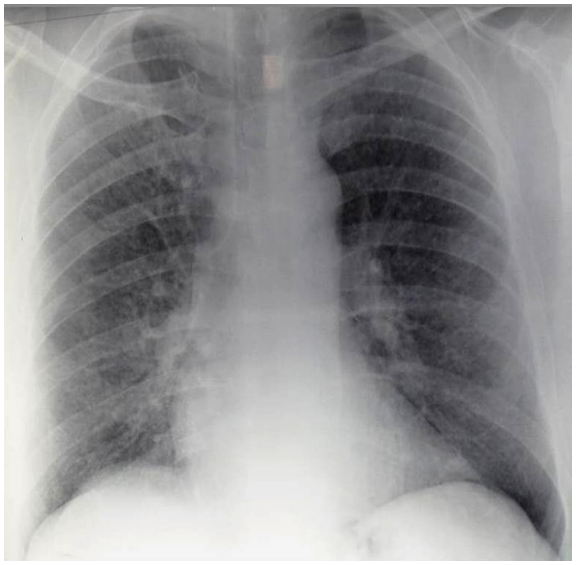

Fig. 1. Chest X-ray revealed bilateral interstitial micronodular pattern.

emergency department with a week-long history of low-grade fever, dry cough, and gradually worsening shortness of breath resulted in severe hypoxemic respiratory failure. The patient was medicated with a daily dosage of 4 g of oral mesalazine. He was also initially treated with intravenous pulse doses of glucocorticoids with a subsequent tapering of prednisolone regimens for a three-month period. Specifically, glucocorticosteroids have been discontinued twenty days before hospital admission. The bowel symptoms remitted within the follow-up intervals. No history of intolerance to salicylates was noted. He had no history of chronic organic solvent or occupational exposures.

On admission, he was apyrexial, hemodynamically stable, tachypnoeic with nineteenth breaths per minute. Lung auscultation revealed non-musical rhonchi bilaterally, especially in middle and lower lung fields. The rest of the physical examination was unremarkable. The chest imaging disclosed a bilateral interstitial micro-nodular pattern (Fig. 1) not revealed in a previous chest X-ray four months ago. High-resolution computed tomography (HRCT) of the chest revealed a diffuse centrilobular ill-defined micronodular pattern (Fig. 2). Arterial blood gas studies performed in resting and breathing from room air showed respiratory insufficiency with pH, partial pressure of oxygen (PaO_2), partial pressure of carbon dioxide ($PaCO_2$), HCO_3 and oxygen saturation (SaO_2) values of 7.46, 51 mmHg, 35 mmHg, 25.8 mmol/L and 85% respectively, while it was observed further deterioration on limited exertion (PO_2: 40 mmHg, PCO_2: 30 mmHg, SaO_2: 81%). The white

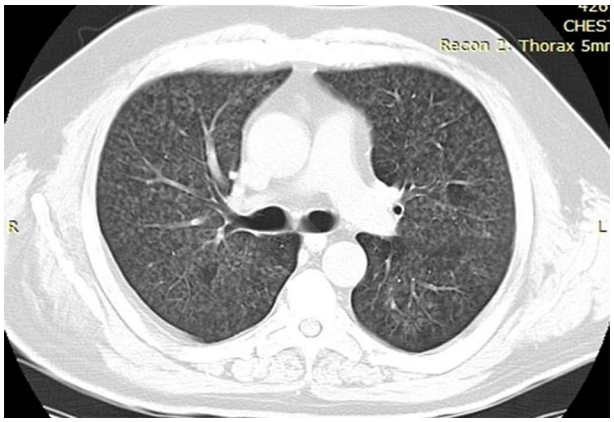

Fig. 2. Chest high-resolution computed tomography. Diffuse low attenuation micronodular pattern.

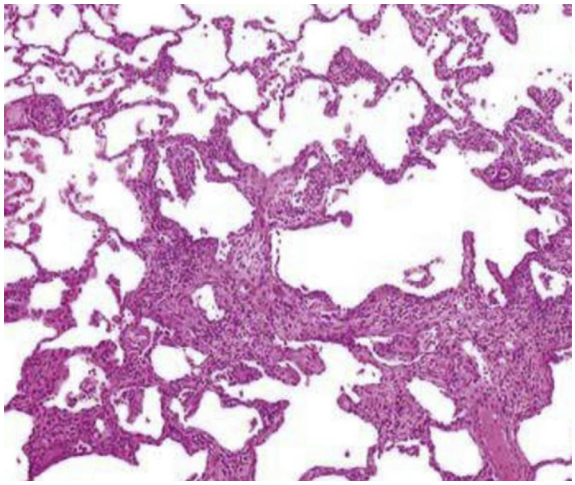

Fig. 3. Photomicrograph of the histopathologic specimen at transbronchial biopsy shows diffuse, bronchiolocentric lymphocytic inflammatory alveolitis (H and E, ×60).

blood cell counted 19.103 per microliter, without peripheral eosinophilia or other increased inflammatory markers.

The differential diagnosis was broad and included miliary tuberculosis, opportunistic lung infections (such as fungal infections, Pneumocystis jiroveci pneumonia, and viral infections), HP, vasculitis, an extra-intestinal manifestation of UC and pulmonary complications caused by mesalazine. Initially, exclusion of infectious etiologies was mandatory, and for this reason, bacterial, fungal, viral and mycobacterial cultures were sent, yielded no isolation of an infectious agent. Bronchoscopy revealed normal airways and the BAL cellular analysis demonstrated a predominance of lymphocytes and an eosinophilia (recovery 60%, macrophages 54.3%, lymphocytes 39.6%, neutrophils 2.3% and eosinophils 3.8%. Lymphocyte CD4+/CD8+ ratio was 1.5. The transbronchial biopsy findings confirmed lymphocytic alveolitis (Fig. 3). Further workup for tuberculosis such as Mantoux test and blood T- SPOT Tuberculosis (T-SPOT TB) test were all negative as well as real-time reverse transcriptase polymerase chain reaction (RT-PCR) for *Pneumocystis jirovecii*, serology for viruses and cytologic exams. Furthermore, pulmonary function tests revealed an obstructive ventilatory pattern (Tiffeneau-Pinelli index: 57% of the expected value and forced expiratory volume in 1 second: 1.18ml, 34% of the expected value). Diffusion of carbon monoxide was not carried out owing to the strong dyspnea affecting the patient. Blood samples were sent for vasculitis screen which were normal. While ceftriaxone and azithromycin given intravenously failed to bring any clinical improvement, the mesalazine withdrawal was decided. After a two-day drug interruption, a surprisingly fast clinical recovery was noticed. Specifically, gas abnormalities remission with an elevation of PaO_2 up to 73 mm Hg and forced expiratory volume-one second (FEV_1) elevation up to 900ml was noticed (FEV1: 1.98ml, 60% of the expected value). In follow up intervals over a two year period the patient was asymptomatic. There was a gradual improvement of chest imaging (Fig. 4) and pulmonary function tests until full recovery within three months. Histopathologic findings obtained by lung biopsy before discontinuation of the drug establish the underlying lung disease process. Subacute HP typically presented with ill-defined nodular opacities in a centrilobular distribution (Fig. 2) that histologically reflect the presence of cellular bronchiolitis, poorly–formed noncaseating granulomas and bronchiolocentric interstitial pneumonitis with a predominance of lymphocytes (Fig. 3). However, in this Case, the lung biopsy was not necessary as the marked clinical and imaging improvement strongly established a relationship between the use of mesalazine and subsequent lung injury.

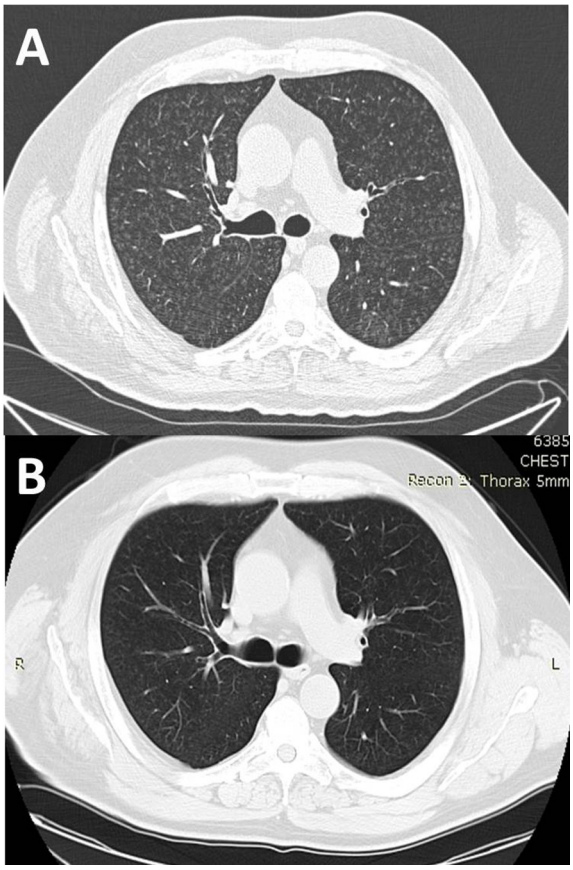

Fig. 4. Resolution of the micronodular pattern after mesalazine discontinuation. A. One month later. B. Three months later.

3. Discussion and conclusions

The first report of mesalazine-induced pulmonary adverse drug reactions in the course of inflammatory bowel disease therapy was described in 1991 [3]. Since then, scattered reports in the literature have underlined the high level of suspicion is needed for the early recognition of this rare pulmonary reaction. However, the pathogenesis of mesalazine-induced pulmonary adverse drug reaction remains unknown. It is postulated that mesalazine causes immune-mediated alveolitis as evidenced by lymphocyte stimulation [4,5], while a dose-dependent direct, direct toxic insult or oxidant injury to the pulmonary epithelium have also been suggested [4,5]. Its histologic reactions observed in biopsies included interstitial lymphocytic infiltrates, alveolar fibrinous exudates, and poorly formed non-necrotizing granulomas, findings that lie within the spectrum of pathology seen in HP, triggered with this agent administered orally [4,5].

Mesalazine-related interstitial lung disease has been previously reported in the form of eosinophilic pneumonia, organizing pneumonia, and nonspecific interstitial pneumonia. Mesalazine-related HP has been scarcely described in the literature [6,7]. Chest radiographs in mesalazine-induced lung injury are nonspecific including interstitial infiltrates, consolidation or pleural effusions. The diffuse micronodular pulmonary pattern presented here is such a seldom imaging finding in Case of mesalazine-related lung injury. Specifically, only Kacprzak et al. have been previously documented a 65-year-old, never-smoking Caucasian woman with UC who presented with a diffuse, ill-defined nodular pattern on HRCT imaging in the course of oral mesalazine treatment although there was no histological confirmation of HP in this case [6]. Furthermore, Sawata T et al. described a 51-year-old woman with Crohn's disease developed drug-induced hypersensitivity syndrome six weeks after starting the oral intake of mesalazine, presented with centrilobular nodular shadows in HRCT [7].

The diagnosis of drug-induced lung injury is challenging for physicians. It is important to distinguish pulmonary manifestations in patients with inflammatory bowel disease secondary to drug-related toxicity as opposed to the disease process itself. Pulmonary involvement in inflammatory bowel disease was described recently as a common complication, with detected changes in pulmonary function [8]. The absence of extra-intestinal manifestations as well as the remission of UC considered to be decisive for the exclusion of pulmonary manifestation of UC.

It has also been documented that the resolution of clinical symptoms and radiologic findings are usually observed within days or weeks from mesalazine discontinuation [3,9,10]. The Case presented here manifested respiratory symptoms after four-month drug therapy. Previous studies reported that the onset of drug reaction varied from days to months after the introduction of mesalazine therapy, with a range of 5 days–44 months [9,10].

Although open lung biopsies are not pathognomonic for drug toxicity and correlation with clinical, laboratory, and radiologic data is required, they can be a tool in the evaluation of suspected interstitial lung disease by helping to exclude underlying disease or infection and documenting the pattern of lung injury; however lung biopsy was not performed in all published cases. Moreover, the role of minimally-invasive procedures, such as BAL or bronchoscopic biopsy is conflictual, as the size of lung tissue samples obtained by transbronchial biopsy is small and the histopathological findings, particularly those that are themselves non-specific, may not be diagnostic [3,9,10]. Conversely, impressive clinical improvement after mesalazine interruption provides strong support for the diagnosis of mesalazine-related lung injury. As far as the drug re-challenge is concerned, it was not performed in this patient because of the initial severity of clinical presentation. In conclusion, this Case indicates that while lung injury is thought to be a rare mesalazine side effect, its possibility should be fully considered when unexplained respiratory symptoms are developed during mesalazine therapy. Amelioration of the symptoms, imaging and lung function improvement, without sequelae, may occur only upon the abrupt drug discontinuation. Although mesalazine-induced HP has been scarcely described in the literature, it constitutes a rare but real entity in UC patients on continuous oral mesalazine treatment.

Declaration of interest

None.

Authors' contributions

Ok conceptualized the Case study, participated in the literature review, was involved in drafting the manuscript, gave final approval of the version to be published. KG conceptualized the case study, had overall responsibility for the manuscript conduction, the critical revision of the case report for important intellectual content and final approval of the version to be published. All authors read and approved the final manuscript.

Consent to publish

Written informed consent was obtained from the patient for publication of this Case report. A copy of the written consent is available for review by the Series Editor of this journal.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmcr.2019.100865.

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