

Acute interstitial lung disease in a patient with ulcerative colitis:

Case report and literature review

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SUMMARY. Mesalazine is widely used for the treatment of idiopathic inflammatory bowel diseases (IBD), such as Crohn's disease and ulcerative colitis. Mesalazine-induced alveolitis is extremely rare, and discrimination between drug-related adverse events and pulmonary manifestations of IBD is difficult. The case is reported of a 45 year-old female with a history of ulcerative colitis, on treatment with mesalazine 500mg three times daily for 10 months, and p-ANCA meningomyelradiculitis, treated with prednisolone, who presented with fever and symptoms of acute respiratory failure. Differential diagnosis included pulmonary manifestations of ulcerative colitis, mesalazine-induced lung toxicity, opportunistic infection, p-ANCA vasculitis and thromboembolic disease. Pulmonary function tests revealed a restrictive pattern with reduced carbon monoxide diffusing capacity, and high resolution computed tomography of the chest showed findings compatible with acute interstitial lung disease. Discontinuation of mesalazine and replacement of oral by iv corticosteroid administration resulted in rapid improvement in the symptoms, radiological findings and pulmonary function tests. *Pneumon 2012, 25(3):320-324.*

INTRODUCTION

Mesalazine (5-ASA) is widely used in the treatment of idiopathic inflammatory bowel disease (IBD), Crohn's disease and ulcerative colitis, because, in contrast with sulfasalazine [SASP; sulfapyridine (SP) bound to 5-aminosalicylic acid (5-ASA)], it does not contain the sulfamidic vector responsible for the adverse effects attributed to the drug¹.

Mesalazine-induced alveolitis is extremely rare, and to date only 10 cases have been described in the English language medical literature. Differentiation between pulmonary involvement in IBD and side effects of mesalazine is very difficult and is based upon a variety of factors, including appearance of symptoms during drug intake, absence of signs of IBD relapse, no history

exposure to other drugs, rapid improvement following drug withdrawal and, in some cases, a history of known hyper-responsiveness to sulfasalazine². The diagnosis may be confirmed histopathologically by transbronchial lung biopsy (TBLB).

CASE REPORT

A 45 year-old non-smoking woman presented at the emergency department complaining of a non productive cough for 10 days, fever up to 38.5°C for 24 hours and rapidly progressive dyspnoea of sudden onset. She had a 10 month history of ulcerative colitis which was being treated with mesalazine 500mg three times daily and was currently in complete remission. She had also been diagnosed 2 years earlier as suffering from p-ANCA meningomyeloculoradiculitis, for which she was on maintenance therapy with prednisolone 5mg/day. On admission, she had a low grade fever, tachypnoea (32 /minute), tachycardia (120 /minute) and mild cyanosis. Auscultation revealed crackling râles in both lower lungs. Blood gas analysis showed severe respiratory failure (PaO₂ 43 mmHg, PaCO₂ 29mmHg, pH 7.49, HCO₃ 23 mmol/L and Sat O₂ 75%, on ambient air). The ECG showed sinus tachycardia and chest X-ray revealed bilateral interstitial thickening and diffuse reticulonodular infiltrates, more pronounced in the lower lobes (Figure 1).

The patient was given combined antibiotic therapy with Clarithromycin 500mg twice daily and Ceftriaxone 2g once daily and supportive fluid and oxygen therapy. Treatment with low molecular weight heparin was initiated to cover the possibility of pulmonary embolism, but mesalazine and prednisolone were not discontinued at this point.

The differential diagnosis included: a) pulmonary embolism (sudden onset of dyspnoea, hypoxaemia with hypocapnia and sinus tachycardia, with a predisposition to deep venous thrombosis because of ulcerative colitis), b) vasculitis (history of positive p-ANCA), c) common or opportunistic infection (treatment with corticosteroids), d) pulmonary manifestations of ulcerative colitis, and e) mesalazine-induced lung damage.

Accordingly, the diagnostic approach included:

- Laboratory tests
- Tuberculin skin testing
- High resolution computed tomography (HRCT) of the thorax
- Pulmonary function tests
- Ventilation-perfusion scan of the lungs

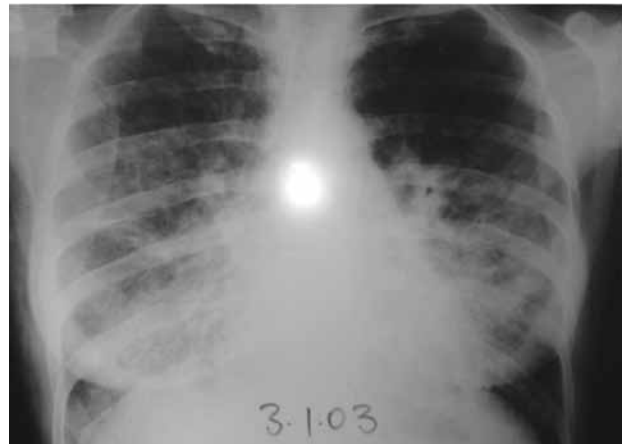


FIGURE 1. Chest X-ray on admission, showing bilateral interstitial and diffuse reticulonodular infiltrates, more pronounced in the lower lobes.



FIGURE 2. High resolution computed tomography (HRCT) of the chest on admission, revealing ground-glass opacities, intralobular and peribronchial thickening, bilateral patchy alveolar infiltrates and vague centrilobular nodules.

- ECHO-doppler of the heart
- Fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) and TBLB

The laboratory findings were unremarkable: WBC 5.60 K/uL (NEUT 84.8%, LYMPH 10.4%, MONO 3.6%, EOS 0.7%), Hb 12.2 g/dl, Ht 37.2%, PLT 289 K/uL, CRP 0.933 mg/dl, ESR 60, Urea 19, creatinine 0.5, SGOT 21 IU/L, SGPT 6 IU/L, γ GT 9 IU/L, LDH 427 IU/L, CPK 15 IU/L, ALP 59 IU/L, Na 145 mEq/L, K 4.1 mEq/L. Further immunological tests were either within the normal range or negative: RA test,

ANA, p- and c-ANCA negative, IgA 293 mg/dl, IgG 1310 mg/dl, IgM 112 mg/dl, IgE 84 U/L. Urine examination was normal and the tuberculin skin test was negative.

Pulmonary function tests revealed a severe restrictive pattern (FEV₁: 2,050ml - 67% of predicted (pred), FVC: 2,110ml - 64.3% pred, %FEV₁: 97.2, FRC: 2,130 ml - 64.9% pred, TLC: 3,480 ml - 68.2% pred) and severely reduced DLCO: 8.36 ml/min/mmHg (pred 25.64).

HRCT showed ground glass opacities in the lungs with geographical distribution, intralobular and peribronchial thickening, bilateral patchy alveolar infiltrates in the anterior lung segments and vague centrilobular nodules crowded in the lower lobes (Fig. 2).

A ventilation-perfusion scan of the lungs was characterized as being of low probability for pulmonary embolism. The ECHO-doppler of the heart was normal (EF of 70 %). The patient declined bronchoscopy.

Although the patient was afebrile 3 days after admission, her respiratory function deteriorated, with an increased need for supplementary oxygen (FiO₂ greater than 0.5%). Treatment with antibiotics was discontinued due to the absence of fever or other signs of respiratory infection. The negative tuberculin test and incompatible radiological findings excluded pulmonary tuberculosis, while the negative p- and c-ANCA and normal renal function tests excluded vasculitis. The normal ventilation-perfusion scan and ECHO-doppler of the heart and the HRCT picture also ruled out pulmonary embolism. The possibility of pulmonary involvement of ulcerative colitis was less likely, as at that point the disease was not manifesting intestinal symptoms.

With the diagnosis of mesalazine-induced alveolitis as the most likely, mesalazine was withdrawn and methyl-prednisolone 1.5 mg/Kg/day iv was instituted, due to the patient's critical condition. Within a few days the patient presented impressive clinical and radiological improvement and normalization of the blood gases (PaO₂ 81 mmHg on ambient air). The pulmonary function tests were also considerably improved (FEV₁: 2,929 ml - 103% pred, FVC: 3,360 ml - 102.5% pred, FRC: 3,100ml - 113% pred and TLC: 4,790 ml - 94% pred), with the exception of DLCO, which remained low (13.23 ml/min/mmHg - 51.6% pred). The patient walked 440m during the 6-minute walking test, with no apparent desaturation by the end of the examination. Chest HRCT performed a week later revealed remarkable improvement of the infiltrates, areas of consolidation and ground-glass opacities (Fig.3).

The patient was discharged on the 12th day, on oral methyl-prednisolone 32mg/day for 15 days with orders for



FIGURE 3. High resolution computed tomography (HRCT) of the chest one week after discontinuation of mesalazine and initiation of corticosteroids, revealing remarkable improvement of infiltrates, areas of consolidation and ground-glass opacities.

gradual tapering off over the next weeks. At follow up at 3-month intervals her spirometry was normal, although the DLCO remained low (14.83 ml/min/mmHg) for a year. After 2 years she presented no residual respiratory symptoms.

DISCUSSION

Sulfasalazine and its active constituent mesalazine (5-aminosalicylic acid, 5-ASA) are usual treatment options in the treatment of IIBD. Although the exact mechanism of action of these drugs remains ill-defined, several potential



FIGURE 4. Chest radiography at 3 month follow up showing normal findings.

mechanisms have been suggested, including interference in arachidonic acid metabolism with subsequent inhibition of mucosal generation of leukotrienes and prostaglandins³, scavenging of free radicals⁴, inhibition of nuclear factor-kappa B (NFκB) and induction of apoptosis⁵.

Although mesalazine lacks the sulfamidic vector responsible for the adverse effects attributed to the sulfasalazine, it has also rarely been incriminated for inducing serious side-effects, such as interstitial nephritis, pancreatitis, blood dyscrasias, hepatitis and skin reactions⁶. Pulmonary complications are extremely rare, and only sporadic cases of interstitial lung disease have been reported; bronchiolitis obliterans organizing pneumonia (BOOP), non-specific interstitial pneumonia, hypersensitivity pneumonitis and pulmonary infiltrates with eosinophilia⁷⁻⁹ and pleural effusion¹⁰.

Respiratory symptoms, most often a non-productive cough, fever and dyspnoea, may appear immediately, a few days after drug initiation¹¹ or several months¹² to 2 years¹³ after initial administration. Lung toxicity does not appear to be dose dependant, as it has been associated with oral doses ranging from 750mg to 4g/day and with topical administration (1g/day) in enema form⁹. In the case reported here, symptoms appeared 10 months after initiation of treatment, when the patient was receiving maintenance therapy in a dose substantially lower than that administered initially.

Blood tests tend to be normal in, but peripheral eosinophilia^{7,12,14} and lymphopenia¹⁵ can be present. In this patient lymphopenia may be attributed either to mesalazine¹⁵ or to the low dose of corticosteroids she was receiving for meningomyelradiculitis. There are also some reports of a positive ANCA^{12,13,16}. Most patients present with mild to severe hypoxaemia that may require supplementary oxygen, and pulmonary function tests show primarily a restrictive pattern with reduced transfer capacity for carbon monoxide (CO)^{9,12,17,18}. Pulmonary findings vary and are non-specific, including segmental, alveolar or nodular opacities, interstitial infiltrates and rarely pleural effusions^{7,10,14,18}. In this case, with the exception of the acute, severe onset, the clinical, radiological and spirometric findings were compatible with the previously reported data. BAL fluid analysis, not conducted here, may be normal or show a lymphocytic or eosinophilic infiltration^{8,14,18-21}. Lung biopsy findings suggestive of chronic interstitial pneumonia or non-necrotising granulomas support the diagnosis²². The prognosis is generally good, with symptoms receding few weeks after withdrawal of the drug, and no deaths have been reported. One patient

required temporary mechanical ventilation²³ and there is a report of long-term residual exertional dyspnoea⁹. The effect of corticosteroids on the short- and long-term prognosis remains unclear, as patients that did not receive steroids responded well to drug withdrawal alone^{17,20}. In the present case, apart from discontinuing mesalazine it was necessary to administer iv corticosteroids due to rapid and progressive deterioration of respiratory failure.

Extraintestinal manifestations of IIBD include arthritis, arthralgia, pericarditis, pyoderma gangrenosum, erythema nodosum, ocular inflammation, pericholangitis, pharyngeal ulceration, venous thrombosis and pulmonary manifestations²⁴. The patterns of respiratory involvement have been described by Camus et al²⁵ and are classified as following: a) airway disease (subglottal stenosis, chronic bronchitis, chronic bronchial suppuration, bronchiectasis, chronic bronchiolitis), b) ILD (BOOP, granulomatous lung disease, pulmonary eosinophilia, c) necrobiotic nodules, and d) pleural effusion. In the majority of patients symptoms occur after the diagnosis of IIBD has been made, and only in exceptional cases are the respiratory manifestations either antecedent to or present concurrently with those of IIBD. The authors reviewed 33 cases (27 with ulcerative colitis and 6 with Crohn's disease; 23 cases receiving no drug therapy). In most cases (28/33), respiratory involvement followed the onset of IIBD (8 of these 28 cases were postcolectomy) and in the remainder, the respiratory manifestations predated the IIBD.

Differentiation between mesalazine-induced lung disease and pulmonary manifestations of IIBD is often challenging for the clinician. In the case reported here symptom onset was acute, with high fever, fatigue and signs of severe respiratory distress. The patient's refusal to undergo bronchoscopy the extremely useful diagnostic tests that could help in documentation of drug toxicity or exclusion of infection in an immunocompromised patient, namely BAL and TBLB²⁶. History of mesalazine exposure in addition to the distinctive radiological findings and the exclusion of other possible lung diseases implied the diagnosis of mesalazine-induced alveolitis, which was eventually confirmed by the rapid clinical and radiological improvement following drug withdrawal. The likelihood that respiratory symptoms could be attributed to lung involvement of IIBD was excluded as the intestinal disease was in remission, manifestations in other organs were absent and symptoms did not reappear during corticosteroid tapering. It should be noted that low dose corticosteroid therapy for another condition did not prevent manifestation of respiratory symptoms,

as has been observed before²². A rechallenge trial with mesalazine reinstatement, although helpful in confirming the diagnosis in previously described cases¹⁹, was not attempted in this patient as it was considered relatively unsafe because of her severe reaction. Rapid improvement in all parameters after drug discontinuation and corticosteroid administration, with no reappearance of the respiratory symptoms in the ensuing years, confirms mesalazine as the causative factor of the lung damage in this patient.

Another challenging feature was the patient's history of p-ANCA positive meningomyelorradiculitis. This complicated the diagnosis, as p-ANCA could give rise to vasculitis presenting with similar clinical and radiological findings, while positive ANCA may also be found during the course of mesalazine-induced alveolitis. In the present case, negative p- and c-ANCA testing and normal renal function excluded this diagnosis.

In conclusion, the possibility of drug-induced lung disease should be always considered in patients with IBD receiving mesalazine who present with respiratory symptoms. Differentiation from pulmonary complications due to IBD can be particularly difficult, as corticosteroids improve lung damage, whether this is generated by the disease itself or is drug-induced.

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