Case Report

Acute organizing interstitial pneumonia and interstitial nephritis due to salazosulfapyridine in a patient with rheumatoid arthritis

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ABSTRACT

Sulfasalazine (salazosulfapyridine) has been used increasingly and successfully for the treatment of rheumatoid arthritis. Azulfidine®EN (salazosulfapyridine; Pharmacia KK Diagnostics, Tokyo, Japan), which dissolves in the intestine, is an improvement over sulfasalazine in terms of diminishing adverse gastrointestinal effects. We report herein a case treated with salazosulfapyridine for rheumatoid arthritis who developed mild dyspnea on exertion, high fever and diffuse pulmonary infiltrates, reversible on discontinuation of the drug. A histologic diagnosis of acute organizing interstitial pneumonia was made by transbronchial lung biopsy. Because the results of a lymphocyte stimulation test against Azulfidine®EN were negative, we allowed the patient to resume Azulfidine®EN for pain in his elbows under informed consent. However, the patient developed symptoms of fever, dry cough and stomatitis and mild renal dysfunction after two doses. Salazosulfapyridine was permanently discontinued and the patient’s symptoms subsided. Laboratory findings returned to normal within 2 weeks. Azulfidine®EN should be added to the list of pharmacologic agents causing infiltrative pulmonary disease and renal dysfunction.

Key words: Azulfidine®EN, drug-induced pneumonitis, interstitial nephritis, rheumatoid arthritis, salazosulfapyridine.

INTRODUCTION

Sulfasalazine (salazosulfapyridine) has been used increasingly and successfully for the treatment of rheumatoid arthritis.1 Adverse gastrointestinal reactions are most common and may affect one-third of patients.2 Azulfidine®EN (Pharmacia KK Diagnostics, Tokyo, Japan), which is an equivalent drug product absorbed preferably in the intestine, is an improvement over sulfasalazine in terms of diminishing adverse gastrointestinal effects. Although several cases of pulmonary infiltrates due to sulfasalazine can be found in the literature,3,4 no similar reactions to Azulfidine®EN have been found. We report herein a case of pulmonary infiltrate and interstitial nephritis induced by Azulfidine®EN during the course of treatment of rheumatoid arthritis.

CASE REPORT

Clinical summary

A 70-year-old man was admitted to the Division of Internal Medicine, Saiseikai Kanazawa Hospital, on 25 April 2000 because of high fever and mild dyspnea on exertion. Chest X-ray on admission revealed diffuse reticulonodular shadows in the bilateral lung fields (Fig. 1). An additional history revealed that the patient had a diagnosis of rheumatoid arthritis since 1992 and had...
undergone bilateral total knee arthroplasty, right total elbow arthroplasty, right wrist arthroplasty (1996), left total elbow arthroplasty (1997), posterior cervical fusion (1998), had been taking 5 mg prednisolone daily and 12 mg methotrexate (MTX) weekly for the treatment of rheumatoid arthritis for 7 months and that in the past 15 days Azulfidine®EN 1000 mg daily had been added. The patient had never smoked.

Physical examination revealed the following: body temperature 36.8°C; blood pressure 110/60 mmHg; heart rate 90 b.p.m. The conjunctivae were not anemic or icteric. Cardiac examination was entirely within normal limits. Auscultation of the lungs revealed late inspiratory fine crackles bilaterally without wheezes or rhonchi. There was no lymphadenopathy. The abdomen was benign and without organomegaly. Severe deformity of the bilateral elbow joints was seen (stage IV; Steinbrocker et al.5).

The white blood cell count was 10,500 /µL with a differential of 87.5% segmented neutrophils, 4.7% lymphocytes, 5.9% monocytes and 1.7% eosinophils. The erythrocyte sedimentation rate was 78 mm/h. The C-reactive protein (CRP) was 26.4 mg/dL, creatinine was 1.1 mg/dL, blood urea nitrogen was 17 mg/dL, rheumatoid factor was negative, the total IgE level was 69 U/mL and KL-6 was 556 U/mL. Arterial blood gas levels while breathing room air were: \( P_{a}O_{2} \) 71.1 mmHg, \( P_{a}CO_{2} \) 44.3 mmHg, \( HCO_{3} \) 30.5 mmol/L and pH 7.45. The following laboratory findings were normal or negative: urinalysis, stools for ova and parasites, serum electrolytes, total protein and albumin, and mycobacterial and fungal cultures of sputum. The electrocardiogram showed normal sinus rhythm.

A chest computed tomography (CT) scan on admission (Fig. 2) showed diffuse ground glass-like opacities with fine reticulonodular shadows in both lung fields.

The pulmonary function test, performed according to the standards of the American Thoracic Society,6 revealed forced vital capacity (FVC) 2.19 L (72.3% of predicted), forced expiratory volume in 1 s (FEV₁) 1.62 L (82.7% of predicted), FEV₁/FVC ratio 74.0%, total lung capacity 3.87 L (85.2% of predicted), residual volume

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**Fig. 1** Chest X-ray on admission revealing diffuse reticulo-linear shadows in the bilateral lung fields.

**Fig. 2** Chest computed tomography scan on admission showing diffuse ground glass-like opacities with fine reticulonodular shadows in both lung fields.
1.62 L (99.4% of predicted), diffusing capacity of the lung for carbon monoxide (DLco) 15.2 mL/min per mmHg (70.6% of predicted) and the gas transfer coefficient (Dlco/VA) 5.11 mL/min per mmHg per L (116.1% of predicted). Because drug-induced pneumonitis was also suspected from the patient’s clinical course, Azulfidine® EN was discontinued and cefazolin sodium (2 g/day) was administered. Within 7 days, the patient’s fever and dyspnea were resolved and CRP decreased to 1.6 mg/dL.

Because the results of a lymphocyte stimulation test against Azulfidine® EN were negative (245 c.p.m./144%), we allowed the patient to resume Azulfidine® EN for pain in his elbows under informed consent. However, he developed symptoms of fever (38.4°C), dry cough and stomatitis and mild renal dysfunction after two doses. Renal biopsy revealed interstitial nephritis. No blood eosinophilia occurred. Azulfidine® EN was permanently discontinued. The patient’s symptoms subsided and laboratory findings returned to normal within 2 weeks (Fig. 3).

Pathologic findings

Bronchoalveolar lavage (BAL) was performed using a total volume of 100 mL sterile saline solution (49% recovery). Cytologic examination showed an increased absolute total cell count of 2.6 × 10⁶ cells/mL and 80% alveolar macrophages, 2% neutrophils and 18% lymphocytes. Bronchoalveolar lavage lymphocyte subsets revealed the presence of CD4⁺ cells (63.3%) and CD8⁺ cells (30.4%). The CD4/CD8 ratio was 2.08.
Transbronchial lung biopsy obtained from the right S8a showed edematous alveolar septa with mild lymphocyte infiltration and intraluminal organization in a fashion of Masson’s bodies (Fig. 4), namely acute organizing interstitial pneumonia.

**DISCUSSION**

A number of drugs have been reported to cause pulmonary infiltrates1–12 and non-steroidal anti-inflammatory drugs have been implicated as etiologic factors for acute interstitial pneumonia.8

Salazosulpyridine has been widely used for the treatment of ulcerative colitis, Crohn’s disease and, more recently, for rheumatoid arthritis.1 Only 15 cases of pulmonary complications induced by this drug have been reported.3,4 Most of cases suffered from inflammatory bowel diseases as described above. Two distinct patterns of pulmonary lesion have been reported: (i) eosinophilic pneumonia;11,12 and (ii) fibrosing alveolitis.13,14 The prognosis of eosinophilic pneumonia is generally good after discontinuation of the causative drug, whereas that of fibrosing alveolitis is less preferable and sometimes fatal in spite of steroid therapy.

In the present case, eosinophils were not seen in the BAL fluid, peripheral blood or the transbronchial lung biopsy specimen. However, the findings of mild alveolitis with tiny luminal organization can be categorized as allergic pneumonitis. The pulmonary lesion in the present case was strictly neither eosinophilic pneumonia nor fibrosing alveolitis, but was not far from these entities. If the discontinuation of the drug was delayed, fibrosing alveolitis could follow.13,14

Although adverse effect profiles of 5-aminosalicylates, such as sulfasalazine and mesalazine, have been categorized for interstitial nephritis, pancreatitis, serious skin reactions, hepatitis and blood dyscrasias, interstitial nephritis was only described for mesalazine.15,16 In the present case, the patient developed mild renal dysfunction after two doses of salazosulpyridine and renal biopsy revealed interstitial nephritis.

It is important to be aware of the possibility of acute organizing interstitial pneumonia occurring in patients treated with not only sulfasalazine, but also Azulfidine®EN, and of interstitial nephritis with not only mesalazine, but also sulfasalazine.

It is well known that 5-aminosalicylates have a wide range of adverse effects. Because the sustained-release formula Azulfidine®EN may also have the same adverse reactions, it is necessary to pay attention to its adverse effects, especially pulmonary and renal complications, when seeing patients receiving this formula.

**REFERENCES**


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