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Title: Sulfasalazine-induced interstitial fibrosis

Running Head: Interstitial fibrosis

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ABSTRACT

Sulfasalazine has been used in the treatment of inflammatory bowel disease for over 60 years. Although the drug is frequently associated with gastrointestinal adverse effects, pulmonary adverse effects are very rare. Herein, we report a case of interstitial fibrosis resulting from 4-month sulfasalazine therapy for ulcerative colitis in a patient under long-term follow-up in our clinic due to chronic obstructive pulmonary disease.

Keywords: Pulmonary fibrosis, sulfasalazine, ulcerative colitis

INTRODUCTION

Sulfasalazine has been used for many years in the management of inflammatory bowel disease. Gastrointestinal adverse effects are common with its use, followed by headaches, arthralgia, cutaneous rashes, hemolytic anemia, leukopenia, and hepatitis. However, sulfasalazine-related

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pulmonary adverse effects are rare. Literature review yielded 50 cases of sulfasalazine-induced pulmonary toxicity, but only 2 isolated cases of interstitial fibrosis were observed since 1972. [1]

In the present case, a patient being followed up for five years due to chronic obstructive pulmonary disease (COPD) exhibited progressive dyspnea and dry cough for one month and was determined to have developed sulfasalazine use-induced interstitial fibrosis. We aimed to share our experiences with this patient, who showed substantial clinical improvement after the discontinuation of sulfasalazine and the initiation of methylprednisolone therapy.

CASE PRESENTATION

A 56-year-old male presented to our clinic with the complaints of progressive dyspnea and dry cough for a month. The patient was being followed up in our clinic for the past five years due to COPD and had been administered sulfasalazine (3 g/day) four months earlier for the treatment of ulcerative colitis. On physical examination, auscultation revealed bilateral basal crepitant rales and slightly prolonged expiration. His respiratory rate was 22 breaths/min, pulse was rhythmic and at intervals of 112 min, body temperature was 36.6°C, and oxygen saturation breathing room air was 64%. Posterior anterior (PA) chest X-ray showed the bilateral areas of consolidation amid ground glass density in all zones, which were most pronounced in the lower zones, and increased fibrotic density bilaterally extending to the pleura in the lower zones (Figure 1). Pulmonary function tests (PFTs) indicated moderate obstruction and mild restriction and diffusion defects (FEV1/FVC=0.62, FEV1=1.82 L [62%], FVC=2.12 L [67%], DLCO=45%; Table 1). Two months before the sulfasalazine therapy was initiated, as per the patient's chest X-ray, only bronchovascular marking was evidently seen (Figure 2), and PFTs showed diffusion limitation and restriction with moderate obstruction (FEV1=1.87 L [65%]; Table 1). High-resolution computer tomography revealed centrilobular and panlobular emphysema in the upper lobes and bilateral fibrotic changes in the basal segments of the lower lobes with sporadic honeycombing (Figures 3 and 4). Extensive ground-glass opacity with the areas of consolidation was observed in both lungs. Radiological findings suggested drug-induced lung disease, and bronchoscopy was scheduled. All lobe and segment bronchi were opened on bronchoscopy; a transbronchial biopsy specimen was obtained from the right middle lobe. The transbronchial biopsy report indicated interstitial fibrosis (Figures 5 and 6). Sulfasalazine treatment was discontinued, and methylprednisolone was initiated at a dose of 1 mg/kg/day. After 1 month of

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the treatment, substantial regression in the areas of consolidation in ground-glass density was observed on PA chest X-ray (Figure 7), and DLCO was 65% in PFT (Table 1). The patient was followed up with a plan to taper the methylprednisolone therapy. Written informed consent was obtained from the patient who participated in this study.

DISCUSSION

Sulfasalazine-induced pulmonary toxicity was first identified in 1972 as pulmonary eosinophilia, and approximately 50 cases have been reported to date. [1] Sulfasalazine is used to treat patients with inflammatory bowel disease at an average dose of 3 g/day for an average duration of 17.8 months. [2] Sulfasalazine-induced pulmonary toxicity may manifest in various forms, including subacute interstitial pneumonia, pulmonary infiltration with eosinophilia, desquamative interstitial pneumonia, bronchiolitis obliterans organizing pneumonia, acute pulmonary edema, eosinophilic pleural effusion, pleural/pericardial hemorrhage or effusion, and antinuclear and anti-histone antibody positivity. [1, 3] More rarely, it may manifest with interstitial fibrosis. The adverse effects due to pulmonary toxicity emerge within approximately 1–32 weeks of the drug use. Our patient began to exhibit symptoms after 16 weeks of the drug use, consistent with the results as per the literature. It has been shown that diffusion limitation detected on PFTs can require up to three years to completely resolve. [4]

There have also been reports of the pulmonary complications of inflammatory bowel disease such as pulmonary vasculitis, bronchiectasis, and pulmonary fibrosis. [5] However, we did not consider these adverse effects possibly because our patient's inflammatory bowel disease was stable when he developed the pulmonary complication, and his symptoms resolved after the discontinuation of sulfasalazine and treatment with methylprednisolone.

Although monitoring alone is usually sufficient after discontinuing the drug, methylprednisolone therapy is preferred for patients with comorbid or life-threatening conditions. [3]

In brief, sulfasalazine-induced pulmonary disease may manifest in different forms. Timely detection and prompt treatment prevent pulmonary complications from developing into a life-threatening situation and permit the avoidance of other drug-related adverse effects. Therefore, an early diagnosis and the treatment of drug toxicity have a major impact on prognosis.

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FIGURES

Figure 1: Posterior anterior X-ray images in the fourth month of the treatment with sulfasalazine. The bilateral areas of consolidation amid ground-glass density in all zones, which were most pronounced in the lower zones, and increased fibrotic density bilaterally extending to the pleura in the lower zones.

Figure 2: Patient's chest X-ray images two months before sulfasalazine therapy only showing evident bronchovascular marking.

Figure 4-5: High-resolution computer tomogram in the fourth month of treatment with sulfasalazine. Centrilobular and panlobular emphysema in the upper lobes and bilateral fibrotic changes in the basal segments of the lower lobes and sporadic honeycombing are observed.

Figure 5: Transbronchial biopsy specimen (hematoxylin–eosin stain; original magnification, ×100). Interstitial fibrosis is observed on the middle lobe.

Figure 6: Masson trichrome (original magnification, ×100); the areas with interstitial fibrosis are shown in green.

Figure 7: Posterior anterior X-ray images after 1 month of the treatment

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Table 1.

PFT	Two months before sulfasalazine therapy	Four months after sulfasalazine therapy	One month after methylprednisolone treatment
FEV1/FVC	0.64	0.62	0.64
FEV1 (L)/(%)	1.87/65	1.82/62	1.85/63
FVC (L)/(%)	2.53/81	2.12/67	2.46/78
DLCO (%)	84	45	65

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