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CASE REPORT

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Mesalazine-Induced Diffuse Lung Injury in a Patient Without Respiratory Signs and Symptoms

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ABSTRACT

Mesalazine is a drug used to treat ulcerative colitis and Crohn's disease, and is known to rarely cause lung injury. We show herein a unique case who developed this drug-induced injury. A 17-year-old boy presented with fever and anorexia after administration of mesalazine. Computed tomography showed extensive ground-glass opacities with peripheral distribution in both lungs. He had general weakness, but had no respiratory symptoms such as cough and dyspnea. With prednisolone, which is primarily aimed at controlling ulcerative colitis, the extensive opacity in both lungs were improved. All patients with this drug-induced lung injury reported to date have had respiratory symptoms, but this patient had no subjective respiratory symptoms and had no abnormalities in respiratory rate and oxyhaemoglobin saturation. Although very rare, we do believe that this clinical course will provide some suggestive information on treatment for patients with similar course in the future.

Keywords: mesalazine, drug-induced, lung injury, ulcerative colitis, Crohn disease.

INTRODUCTION

Mesalazine is a drug that treats ulcerative colitis (UC) and Crohn's disease (1). Very rarely, this drug is known to cause lung injury (2-11). The mechanism is assumed to be direct drug-induced damage to type II alveolar epithelial cells and vascular endothelial cells, and drug-induced activation of immune system cells (12). With the exception of some patients with central bronchiectasis and bronchiolitis (2, 3), most of the patients had lung involvement with diffuse lung opacities (4-11). For this rare adverse event, it is necessary to differentiate between pulmonary infections of va-

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rious micro-pathogens or pulmonary complications due to UC itself (4-11). In critical cases with a typical clinical-radiological and temporal presentation, the initiation of therapy should not be delayed by an elaborate diagnostic approach. It is extremely difficult to differentiate between these conditions. Imaging findings, pathological histopathology, drug administration status and disease control status of UC can be useful in the differential diagnosis of other diseases, but are not direct diagnostic evidence (13). Some patients with this drug-induced lung injury were critically ill patients requiring supplemental oxygen and mechanical ventilation (8, 10, 11) and other patients had respiratory symptoms but did not require such treatment (6, 9). Patients with severe respiratory failure may not tolerate bronchoscopic tissue sampling. In such cases, it is necessary to decide whether to discontinue mesalazine and, if necessary, administer prednisolone.

We herein report a case with lung injury due to mesalazine in a patient with poorly controlled UC. Patients with this drug-induced lung injury reported to date have had respiratory symptoms, but this patient had no subjective respiratory symptoms and had no abnormalities in respiratory rate and oxyhaemoglobin saturation. In the case of rare diseases, the accumulation of clinical information by case reports might provide valuable data for the management of such disorders.

CASE REPORT

A 17-year-old boy who had been complaining of diarrhea and bloody stool for two months was referred to our hospital. Following a diagnosis of pancolitis type UC after colonoscopy, the patient was prescribed oral mesalazine at 4.5 g/day. Two weeks after the initiation of this treatment, he addressed our hospital because of persistent anorexia and development of fever, but had no respiratory symptoms such as cough, sputum and dyspnea. On admission, body temperature 38.0 °C, blood pressure 110/70 mm Hg, respiratory rate 16/min, SpO_2 98% (room air). Chest auscultation showed no heart murmurs and no accessory rales. The abdomen was flat and soft, and intestinal peristaltic sounds were reduced. No edema in extremities. Laboratory evaluation revealed white blood cell count of 6,500/mm^3 with 78% neutrophils, 8% lymphocytes, and 4% eosinophils, hemoglobin of 7.0 g/dL, and platelet count of 3,270,000/mm^3. The serum levels of c-reactive protein were 15.26 mg/dL and erythrocyte sedimentation rate was 112 mm/h. Blood urea nitrogen levels were measured at 8.0 mg/dL and creatine 0.86 mg/dL. Liver-related tests revealed an alanine aminotransferase of 5IL/L, aspartate aminotransferase of 15IL/L, alkaline phosphatase of 71 IU/L, total bilirubin level of 0.4 mg/dL. Cryptococcal antigen, *Aspergillus* antigen and β-D-glucan (<5.0 pg/mL) were negative. Test results for antinuclear antibodies and myeloperoxidase antineutrophil cytoplasmic antibody were negative. Blood and urine cultures were performed to rule out infectious diseases. A computed tomography (CT) scan performed at the time of admission showed diffuse ground-glass opacities in both lungs with peripheral distribution, especially in the lower lobes (Figure 1). Due to persistent diarrhea and bloody stools, intravenous hyperalimentation was started for the purpose of intestinal rest. Broad-spectrum antibiotic was administered, but there was no improvement. Based on the results of the above-mentioned examinations, no response to antibiotics and the absence of respiratory symptoms, we concluded that mesalazine-induced lung injury was highly

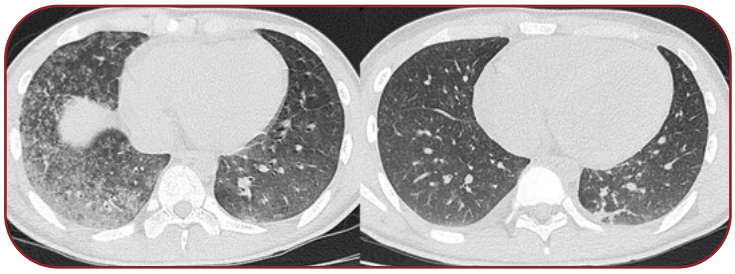

FIGURE 1. Chest computed tomography scan performed at the time of admission showed diffuse ground-glass opacities in both lungs with peripheral distribution.

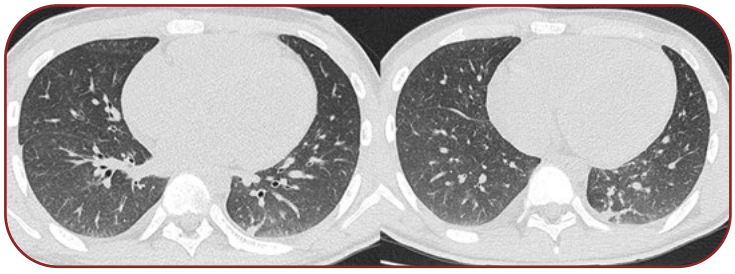

FIGURE 2. Chest computed tomography taken two weeks after the initiation of prednisolone therapy revealed reduction in the mosaic attenuation.

probable and mesalazine administration was discontinued. Then, taking into account the nutritional status and general condition of the patient, prednisolone 40 mg/day was initiated. A few days after the start of prednisolone, fever disappeared and chest imaging improved (Figure 2). He was transferred to a university hospital for treatment of UC with Infliximab. After transfer, a lymphocyte stimulation test for mesalamine in the blood was found to be negative. This result was probably due to the fact that prednisolone had been started.

DISCUSSION

We reported a case with mesalazine-induced lung injury in a patient with poorly controlled UC. Lung injury developed five days after the start of mesalazine administered at 4.5 g/day. The distribution of the injury was dominant in both lower lobes with peripheral distribution. There was no decrease in oxyhaemoglobin saturation, but prednisolone was administered in addition to mesalazine withdrawal due to his general condition. As a result, rapid improvement in lung opacities was observed, but UC was not sufficiently controlled. Notable features of this case were the lack of subjective symptoms or decrease in oxyhaemoglobin saturation despite the presence of diffuse ground-glass opacities in both lungs on chest CT scan. In two reviews and recent case reports, it was described that patients with respiratory involvement of ulcerative colitis were accompanied by symptoms such as coughing and dyspnea (14-17). There was one exception, this patient without respiratory symptoms was a patient with bilateral lung masses (18). Even in lung infections in patients with ulcerative colitis, it is almost always accompanied by some kind of respiratory symptoms (17). Although there was a diffuse ground-glass opacification on the CT image, he was asymptomatic and had no decrease in oxygen saturation, therefore, we determined that the most appropriate diagnosis for this patient was mesalazine-induced diffuse lung injury. Prednisolone was introduced to control the primary disease rather than to improve incidental respiratory findings. As a result, although a marked improvement was obtained on chest CT, the improvement in ulcerative colitis was insufficient, and the patient was transferred to another hospital for other treatment. As far as we could document, 38 patients with mesalazine-induced lung injury have been reported (2-11). All of these patients had cough and dyspnea without a decrease in oxyhaemoglobin saturation or arterial oxygen partial pressure. Among patients with mesalazine-induced interstitial lung disease there are cases with parenchymal involvement but no respiratory symptoms or respiratory failure.

In previously reported patients with mesalazine-induced lung injury, their median age was 50 (range: 14-75) years, and 15 were males and 23 were females (4-11). In 31 patients for whom data were available, the median daily dose of mesalazine was 2.25 (range: 0.75-4.8) g. Of the 16 patients with less than 2.25 mg/day, 11 had prednisolone and 10 of the 15 patients with ≥2.25 mg/day had prednisolone ($p=0.999$, chi-square test) (4-11). In 33 patients for whom data were available, the median duration of mesalazine administration was 30 days (range: one day–five years) in patients for whom data were described. Prednisolone was administered in 12 out of 16 patients for less than 30 days, and 10 out of 17 patients for 30 days or longer ($p=0.465$, chi-square test) (4-11). The chest CT images seen in mesalazine-induced lung injury were diverse, and it has been evaluated that there were no findings specific for this lung injury regarding the distribution and spread of opacities, with the exception of some patients with central bronchiectasis and bronchiolitis (2, 3). Of the 25 patients with diffuse lung opacities, to our best knowledge, 23 had consolidation and/or ground-glass opacity and three, nodular opacities (4-11). Fifteen patients had bilateral opacities and six of them diffuse opacities in all the lobes. Ten patients had unilateral opacities (4-11). Thirteen patients were described as having upper lobe predominance and four patients as having lower lobe predominance (4-11). Thirty-four reports described pathological diagnosis using lung biopsy specimens: 13 interstitial pneumonia, 12 eosinophilic pneumonia, seven organizing pneumonia and two hypersensitivity pneumonitis (4-11). There were patients whose opacities do not necessarily occur diffusely on both lungs. Therefore, it is meaningful to differentiate lung injury caused by this drug even in the absence of diffuse opacities on both lungs. It should also be

noted that there are no pathological findings that were characteristic or specific to this lung injury.

Mesalazine-induced lung injury includes both asymptomatic patients, such as our patient, and patients requiring mechanical ventilation. Although rare, some patients have been reported to have improved simply by discontinuing mesalazine without the need for prednisolone (9). The prognosis of this lung injury is supposed to be good, although the presence of publication bias must be considered. Given the above, the indications for prednisolone are firmly established. Therefore, at this time, mesalazine should be withdrawn first in patients with mesalazine-induced lung injury. We do believe that prednisolone should be administered without hesitation to patients with respiratory symptoms and signs of respiratory failure. If a response is obtained, prednisolone should be rapidly tapered and then discontinued. We reported this case for the purpose of providing information that contributes to the management of patients with this pathology. ❑

Statement of ethics: This study was approved by the institutional ethics committee of our institute (NO 1639). Written comprehensive informed consent at the time of admission for obtaining pathological specimens was obtained from the patient.

Conflicts of interest: none declared.

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Authors' contributions: YM and HS designed the study; YM, KO, HA, JK and HS analyzed the data; YM and HS prepared the manuscript; JK and HS supervised this study. All Authors approved the final version for submission.

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