Drug Rash with Eosinophilia and Systemic Symptoms Syndrome in a Patient on Sulfasalazine for Ulcerative Colitis

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Drug rash with eosinophilia and systemic symptoms (DRESS) is a life-threatening systemic drug reaction characterized by fever, rash, hematological abnormalities, lymphadenopathy, and multiple internal organ involvement. Unfortunately, a long latency period as well as clinicians’ unawareness of the disease entity often results in a delay of prompt diagnosis and treatment in clinical practice. A search of the literature revealed only few reports on DRESS in patients with inflammatory bowel diseases. The pathogenesis of the disease is not clearly understood, although several possible mechanisms, such as drug detoxification, slow acetylation, and reactivation of human herpes viruses, have been proposed in its development. Here, we present a rare case of DRESS associated with viral reactivation and defects in drug metabolism in a 22-year-old man who had been on sulfasalazine for 6 weeks to treat ulcerative colitis. (Intest Res 2012;10:383-387)

Key Words: Drug Eruptions; Hypersensitivity; Sulfasalazine; Human Herpes Virus; Ulcerative Colitis

INTRODUCTION

Drug rash with eosinophilia and systemic symptoms (DRESS) is a rare but potentially fatal hypersensitivity reaction characterized by fever, rash, hematological abnormalities, lymphadenopathy, and multiple internal organ involvement. DRESS characteristically arises after a long latency period of 2 to 6 weeks. The estimated incidence of DRESS ranges between 1:1,000 and 1:10,000 drug exposures, but a recent research in Korea suggested that the syndrome is more common than generally recognized. Although a clinical overlap may exist with other severe drug eruption syndromes, DRESS has been considered to be a distinct disorder with unique characteristics. Notably, the mortality rate from DRESS has been reported to be as high as 10%; therefore, prompt diagnosis is essential to improve the prognosis.

Sulfasalazine is one of the essential drugs used for the treatment of IBD as well as rheumatic diseases such as rheumatoid arthritis and spondyloarthropathies. While many studies have described experiences of sulfasalazine-induced DRESS in rheumatic diseases, few such reports have examined in relation to IBD. We herein describe a case of DRESS on sulfasalazine treatment of UC for 6 weeks and present a short review of the literature.

CASE REPORT

A 22-year-old man presented with a sudden onset of symptoms consistent with viral infection, including fever, chills, myalgia, and generalized skin rash. He had been taking 4.5 g of sulfasalazine for 6 weeks to treat newly diagnosed UC from the referring hospital. Fever and skin rash developed 2 weeks before admission to our hospital. Skin eruptions presented first on the trunk, followed by the rest of the body. The patient denied any history of drug allergy. On admission, body temperature was 38.5°C, blood pressure was 110/80...
mmHg, and heart rate was 90 beats/min. The physical examination showed a widespread morbilliform maculopapular skin eruption in the trunk and limbs, which consisted of 1-3 mm sized erythematous lesions (Fig. 1) and facial edema. He had a non-tender, palpable spleen 3 cm below the left costal margins. However, hepatomegaly and lymphadenopathy were not definite. Initial complete blood cell counts showed leukocytosis of 18,880/μL (polymorphonuclear leukocytes 29%, lymphocytes 41%, atypical lymphocytes 12%, and eosinophils 4%), hemoglobin of 10.2 g/dL, and platelets of 313,000/μL. On peripheral blood smear, moderate leukocytosis with atypical lymphocytosis was noted (Fig. 2). Other laboratory findings were as follows: high LDH (1,655 IU/L [normal, <195 IU/L]), liver cytolysis (AST, 119 IU/L [normal, <18 IU/L] and ALT, 115 IU/L [normal, <19 IU/L]), moderate cholestasis (alkaline phosphatase, 800 IU/L [normal, 21-85 IU/L] and γ-GT, 519 IU/L [normal, <45 IU/L]), increased CRP (2.28 mg/dL [normal, <0.3 mg/dL]), normal erythrocyte sedimentation rate (8 mm/hr [normal, <15 mm/hr]), and increased serum IgE (IgE, 969 IU/mL [normal, <100 IU/mL]). No bacteria were found in multiple cultures from blood, urine, and stool. Pulmonary radiography was unremarkable, but abdominal CT revealed hepatosplenomegaly (Fig. 3) and multiple intra-abdominal lymphadenopathies (Fig. 4). The colonoscopic findings revealed mild erythema and loss of vascularity with fine granularity in the rectosigmoid colon, suitable for mild ulcerative proctosigmoiditis (Fig. 5). Initially, the patient received ceftriaxone for empirical broad coverage of bacterial infections, but he clinically deteriorated during the next 3 days.

To exclude potential viral infection, we performed serological tests for hepatitis B, hepatitis C, human immunodeficiency viruses, parvovirus B19, herpes simplex viruses 1 and 2, cytomegalovirus (CMV), Epstein-Barr virus (EBV), and human herpes virus 6 (HHV-6). The positive results were as follows: IgG anti-viral capsid antigen (VCA) (1:36), IgM anti-VCA (1:9), IgG anti-Epstein-Barr nuclear antigen (EBNA) (1:70), and IgG anti-HHV-6 (1:320). Other results were negative. A punch biopsy taken from the skin of his right lower leg revealed lymphocytic vasculitis and interface dermatitis, suggestive of drug-induced hypersensitivity (Fig. 6). From these findings, DRESS associated with sulfasalazine was strongly suspected. Finally, all findings met the current proposed diagnostic criteria of DRESS. Therefore, sulfasalazine was immediately withdrawn and the patient was treated with intravenous corticosteroids (1 mg/kg of prednisolone equivalent per day). Fever and myalgia resolved greatly within 3 days, and the patient was discharged with oral prednisolone.
on the fifth hospital day. However, the generalized erythematous rash remained without improvement. At 4 weeks, the skin rash disappeared completely and laboratory abnormalities normalized. Throughout the 6 months after switching sulfasalazine to 5-aminosalicylic acid, the patient remained well without recurrence of skin rash or systemic symptoms associated with DRESS.

**DISCUSSION**

Sulfasalazine was originally proposed as a treatment for rheumatic diseases, but it has been widely used to treat IBD, particularly UC. To date, several cases of sulfasalazine-induced DRESS in rheumatic diseases have been reported, which is extremely rare in IBD. To our knowledge, only two cases of sulfasalazine-induced DRESS have been reported in IBD in the literature that had clinical features similar to ours.

In patients with DRESS, hepatitis, lymphadenopathy, and hematological abnormalities are observed to varying degrees. These diverse presentations emphasize the need for a set of diagnostic criteria that are easily applicable in the clinical setting. At present, no gold standard for diagnosis exists, but at least two diagnostic criteria have been proposed: the Japanese consensus group criteria and the RegiSCAR criteria. In the present case, liver injury, cholestasis, lymphadenopathy, and atypical lymphocytosis were noted even when peripheral eosinophilia did not occur. The skin rash of our patient developed 6 weeks after the initiation of the offending drug and remained for 4 weeks despite the withdrawal. The combination of widespread skin eruption with clinical heterogeneity met the diagnostic criteria of DRESS, as mentioned above. These clinical features of a long latency period and persistence of manifestation even after withdrawal of culprit drugs are unique characteristics that implicate DRESS as a distinct disorder and distinguish it from toxic epidermal necrosis and Steven-Johnson syndrome. DRESS is difficult to differentiate from infectious mononucleosis since
rash, fever, lymphadenopathy, hepatosplenomegaly, atypical lymphocytosis and viral activation are present in both conditions. However, in this particular case, the patient’s medical history of sulfasalazine usage, the results of skin biopsy and the patient’s clinical symptoms such as facial edema and morbilliform rash which were evident even after subsidence of fever and myalgia all pointed to DRESS rather than infectious mononucleosis.

However, the pathogenesis of DRESS has not been fully elucidated. Sulfasalazine is a Sulfonamide-containing compound and is subjected to cleavage by the colonic flora to yield its two metabolites: 5-aminosalicylic acid and sulfapyridine. The accumulation of toxic metabolites due to slow acetylation of sulfapyridine in the liver, which is genetically determined, has been associated with an increased risk of DRESS, highlighting the importance of drug metabolism and genetic predisposition. These metabolites may activate macrophages, eosinophils, and T cells, which result in the release of cytokines, mainly interleukin-5, which explains drug hypersensitivity. Interestingly, our patient has taken 5-aminosalicylic acid instead of sulfasalazine during the 6-month period of follow-up period, but a relapse of DRESS, evident by symptoms, was not detected. This fact may also suggest that sulfapyridine is the causative metabolite in the pathogenesis of DRESS.

In susceptible people, a transient drug-induced hypogammaglobulinemia has been proposed to create an immunological environment that permits viral reactivation. Recent studies and case reports showed that DRESS may be associated with activation of members of the HHV family, namely HHV-6, EBV, and CMV. Other recent investigations using PCR of viral DNA identified early reactivation of HHV-6 and EBV, with later involvement of HHV-7 and CMV. Among HHV, the most convincing data regarding the association of viral infection and DRESS concern HHV-6. HHV-6 reactivation has been recently proposed as one of the criteria for confirmation of DRESS. The long latency period after starting therapy with causative drugs may represent the time required for immunoglobulin levels to decrease lower than the threshold level for viral reactivation. In the present case, we identified interesting findings of reactivation of HHV-6 and EBV through the dynamics of the serological studies including a high IgG anti-HHV-6 titer and the presence of IgG anti-EBNA, IgG, and IgM anti-VCA. These findings make our case unique, since two cases of sulfasalazine-induced DRESS in IBD did not exhibit the above-mentioned results. Indeed, it is difficult to demonstrate whether viral infection is a prerequisite for DRESS or an outcome of immune dysfunction in DRESS. Therefore, a large prospective study is necessary to investigate the role of the HHV family.

The mortality rate from DRESS has been estimated at 10%, with most patients dying from liver failure. Therefore, early diagnosis and appropriate treatment are essential. At present, the optimum treatment of DRESS remains unclear. Current management of DRESS generally includes discontinuation of the culprit drug and treatment with systemic corticosteroids. However, no antiviral treatments have been suggested despite the evidence for a role of HHV. In the present case, sulfasalazine was immediately withdrawn and the patient was treated with intravenous corticosteroids. The clinical symptoms resolved rapidly, but the skin rash remained during hospitalization. After discharge, both the skin rash and laboratory abnormalities were gradually normalized with corticosteroid taper without relapse.

In conclusion, we have reported a rare case of sulfasalazine-induced DRESS associated with the reactivation of HHV-6 and EBV in IBD. The reactivation of HHV implies that viral serology should be performed in patients with suspected DRESS. Besides early recognition of DRESS, withdrawal of the culprit agents is essential in the management of DRESS. Further collaborative research driven by clinical networks is needed to elucidate the disease pathway and recommend specific treatment guidelines.

REFERENCES


