A case of drug reaction with eosinophilia and systemic symptoms with colitis as a presenting feature

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INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a potentially life-threatening hypersensitivity reaction characterized by skin eruption, fever, hematologic abnormalities, lymphadenopathy, and end-organ damage. Involvement of the gastrointestinal tract has only rarely been reported in the literature. We report a case of sulfasalazine-induced DRESS manifesting as colitis.

Abbreviations used:

AGEP:	acute generalized exanthematous pustulosis
DRESS:	drug reaction with eosinophilia and systemic symptoms
RA:	rheumatoid arthritis
RegiSCAR:	Registry of Severe Cutaneous Adverse Reactions
SCAR:	severe cutaneous adverse reaction

CASE REPORT

A 42-year-old woman with a past medical history of rheumatoid arthritis (RA), managed with hydroxychloroquine monotherapy for many years, presented to our hospital with fever, abdominal pain, and diarrhea lasting for 2 weeks. On admission, a computed tomography scan of her abdomen revealed diffuse colitis with extensive abdominal lymphadenopathy. Broad-spectrum antibiotic therapy was initiated for a presumed infectious etiology. On hospital day 4, she was noted to have a diffuse cutaneous eruption, and dermatology was consulted for evaluation. The patient reported that the eruption had begun several days prior to the admission, when she noticed small papules on her face. The eruption was pruritic but painless and had progressed to involve her trunk and extremities during her course of hospitalization. She reported having started sulfasalazine 500 mg twice daily 4 weeks previously for RA.

Physical examination revealed diffusely scattered 2-4-mm erythematous papules on the trunk and upper extremities, with surrounding erythema and diffusely scattered 1-2-mm pustules (Fig 1, *A* and *B*). Marked facial erythema was present, as well as submandibular and cervical lymphadenopathy. No mucosal involvement was observed. The patient was febrile (38.7 °C), and laboratory studies revealed leukocytosis (white blood cell count, 19.8 $\times$ 10^9/L) with eosinophilia (2.6 $\times$ 10^9/L), neutrophilia (12.5 $\times$ 10^9/L), and atypical lymphocytosis (0.4 $\times$ 10^9/L). Creatinine was elevated (1.95 mg/dL), as were liver enzymes (aspartate aminotransferase level, 72 U/L; alanine aminotransferase level, 89 U/L). Results for hepatitis A, hepatitis B, hepatitis C, HIV, blood cultures, *Clostridium difficile*, SARS-CoV-2, Epstein-Barr virus, *Candida*, blood parasites, *Brucella*, tuberculosis, cytomegalovirus, *Strongyloides*, human herpes virus 6, superficial wound culture, and a gastrointestinal pathogen polymerase chain reaction panel were all negative. Colonoscopy revealed pancolitis with congested, inflamed, and ulcerated mucosa in the entire portion of the colon examined.

Colon biopsy specimens revealed active colitis with crypt abscesses and infiltration of the lamina propria by neutrophils, eosinophils, histiocytes, lymphocytes, and plasma cells. Additionally,

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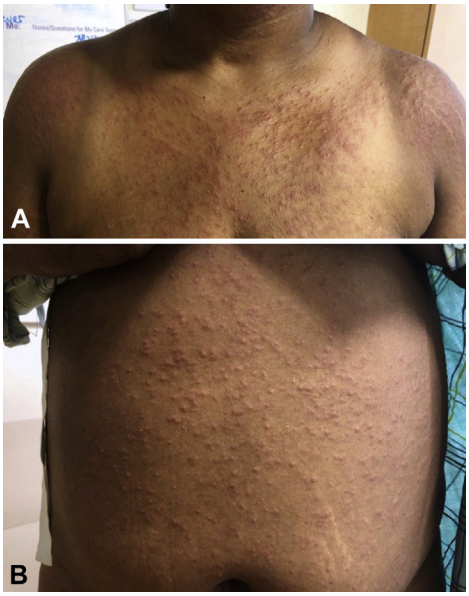

Fig 1. Clinical morphology of new-onset eruption on the (**A**) chest and (**B**) abdomen in the setting of pancolitis.

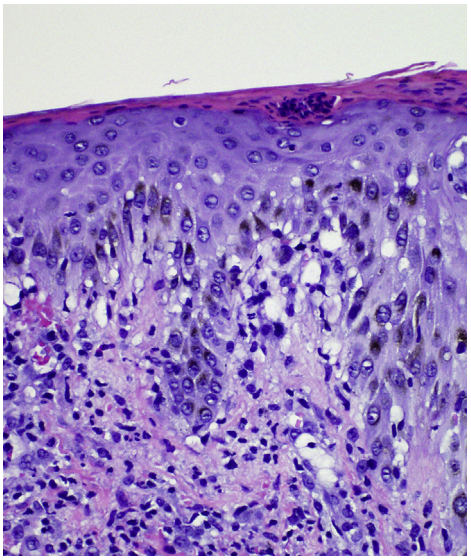

Fig 2. A mixed-cell infiltrate of lymphocytes and neutrophils with interface changes and a small subcorneal microabscess. (hematoxylin-eosin stain; original magnification: ×400.)

minimal crypt architectural distortion was noted. Serologic studies, stool studies, and blood examinations performed to rule out pathogenic organisms were negative. A skin biopsy from the back revealed a perivascular and perifollicular mixed-cell infiltrate of lymphocytes with scattered neutrophils, interface changes, spongiosis, and a small subcorneal collection of neutrophils (Fig 2).

By applying the European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) scoring system, a diagnosis of DRESS syndrome secondary to sulfasalazine was established. A RegiSCAR score of 8 places the patient in the "definite case" category for DRESS syndrome. Sulfasalazine was held, and the patient was started on intravenous methylprednisolone and topical corticosteroids. Within 3 days of treatment, the patient defervesced, and diarrhea and abdominal pain resolved. The cutaneous eruption, hematologic abnormalities, and liver dysfunction gradually resolved over the subsequent 3 weeks during a taper of oral corticosteroids. At the 6-month follow-up visit, the patient had no relapses of her cutaneous eruption and no recurring episodes of diarrhea to report.

DISCUSSION

DRESS syndrome is a potentially life-threatening drug-induced hypersensitivity reaction that classically occurs 2 to 6 weeks after initiation of an offending drug. The most common causative drugs include antiepileptics, allopurinol, sulfonamides, and vancomycin.[1] The syndrome commonly manifests with a cutaneous eruption, hematological abnormalities, lymphadenopathy, and internal organ involvement. The liver, lungs, and kidneys are commonly affected in DRESS syndrome, but involvement of other organ systems is possible.[2] Unusual presentations involving the ocular, cardiovascular, endocrine, and neurologic systems have been described. Involvement of the gastrointestinal tract has only rarely been reported, largely in the context of antiepileptic medications.[3-6] To our knowledge, this is the first reported case of DRESS manifesting as colitis and caused by sulfasalazine.

In the few reported cases of DRESS syndrome with colitis, biopsy of the gastrointestinal tract has demonstrated predominantly eosinophilic infiltrates.[4,5] In contrast, our patient's colon biopsy had a mixed infiltrate of neutrophils, eosinophils, histiocytes, and lymphoplasmacytic cells. Additionally, this patient's cutaneous eruption exhibited scattered minute sterile pustules, with dermal and subcorneal neutrophils seen on skin biopsy, raising the possibility of acute generalized exanthematous pustulosis (AGEP). Although DRESS syndrome typically presents with a morbilliform eruption, a broad spectrum of cutaneous morphologies has been described. In one prospective study, pustules were noted in 30% of DRESS cases.[1]

Although the histopathological features of DRESS syndrome are known to be variable and nonspecific, the histopathology of AGEP is characterized by the presence of sterile nonfollicular subcorneal pustules.[7] Notably, AGEP is known to present with

both quick onset after drug exposure (usually within 24-48 hours), which was not a feature of this case, and with rapid resolution after drug cessation. Systemic involvement is much less common in AGEP, with one retrospective study observing 17% of AGEP cases with visceral involvement; most commonly of the liver, kidneys, and lungs.[8,9] To date, there have been no reports of AGEP-related colitis. The possibility of overlap conditions between DRESS and other severe cutaneous adverse reactions (SCARs) such as AGEP and Stevens–Johnson syndrome/toxic epidermal necrolysis has been questioned in the literature.[7] In fact, in the acute stage of SCARs, discrimination between AGEP, DRESS, and Stevens–Johnson syndrome/toxic epidermal necrolysis can be challenging because of overlapping clinical features. For example, even when applying the EuroSCAR criteria for AGEP in this case, the final score falls within the probable but non-definitive range. In some cases, classification between different SCARs is only possible through retrospective clinical reasoning.

Immediate withdrawal of the offending drug is first-line therapy in DRESS syndrome. For patients with features of severe DRESS syndrome (transaminase levels greater than 5 times the normal, any renal involvement, pneumonia, or hemophagocytosis), systemic corticosteroid treatment (0.5-1 mg/kg/day) is often recommended, although there is a lack of large-scale data to support a defined therapeutic algorithm.[10] In this patient's case, drug discontinuation and high-dose systemic corticosteroids led to resolution of the cutaneous eruption, laboratory abnormalities, and colitis. This case highlights how colitis may be a manifestation of DRESS syndrome and should be considered in the appropriate clinical setting to ensure timely diagnosis and intervention.

Conflicts of interest

None disclosed.

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