

Drug hypersensitivity syndrome with significant gastrointestinal involvement

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ABSTRACT Drug hypersensitivity syndrome (DHS) is an idiosyncratic systemic reaction to a drug. The clinical presentation of this syndrome comprises a diverse spectrum, ranging from mild to fulminating organ failure. Nonspecific gastrointestinal symptoms are common in DHS, but severe morbidities and mortalities attributed to gut disease in DHS are rarely described. We present a case of DHS with significant gastrointestinal symptoms of prolonged profuse watery diarrhoea and persistent hypokalaemia requiring judicious intravenous water and electrolyte replacement. The symptoms resolved only after the introduction of intravenous hydrocortisone. It is important to consider intravenous corticosteroids if the gastrointestinal system is involved, as accelerated gut motility and mucosal damage would affect absorption of oral medications. Supportive treatment with the monitoring of fluid and electrolytes status and judicious replacement remains fundamental in the management of DHS patients with gut involvement.

Keywords: colitis, drug hypersensitivity syndrome, oesophagitis, gastrointestinal
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INTRODUCTION

Drug hypersensitivity syndrome (DHS) is one of the many terms used to describe an idiosyncratic systemic reaction to a drug. DHS presents as a spectrum, ranging from a mild rash with transient eosinophilia and lymphadenopathy, to fulminating organ failure.^(1,2) Few cases of extensive gastrointestinal tract involvement in DHS have been reported.⁽³⁾ We present a case of DHS with significant gastrointestinal symptoms. The diagnosis is based on the criteria set by the European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) study group.⁽⁴⁾

CASE REPORT

A 52-year-old Malay woman presented with a one-week history of maculopapular rash over the trunk and limbs, which was associated with severe oral mucositis, and mild facial oedema and high fever a week after she was treated with amoxicillin-clavulanic acid for otitis media. She had concurrent profuse, non-bloody diarrhoea at a minimal daily frequency of ten episodes for at least a week. There was no eye or genital involvement. She had leucocytosis, peaking at a level of $21.1 \times 10^3/\mu\text{L}$, which was associated with 12% of atypical lymphocytes with no eosinophilia. There was hyperbilirubinaemia and transaminitis, with liver enzyme levels at three times the norm. Renal, thyroid and autoimmune screens were unremarkable. Microbial and viral studies, including human herpesvirus (HHV)-6, were negative. The skin histology of the patient was consistent with a drug reaction, with interface change and no evidence of epidermal necrosis. Both direct and indirect immunofluorescence studies were negative.

The patient was diagnosed with DHS. She was started on oral prednisolone at 1 mg/kg per day. Her oral ulcers improved

rapidly with the initiation of oral corticosteroids, but her truncal and limb rashes were slow to respond. In addition, she continued to spike high temperatures and had persistent profuse watery diarrhoea, which resulted in hypokalaemia that required daily intravenous replacement. Stool analysis revealed leucocytes, but cultures were unremarkable. Colitis was absent on abdominal computed tomography imaging. The gastroenterologists attributed her diarrhoea and transaminitis to a drug reaction, and planned for endoscopic investigations.

Despite ten days of high dose oral prednisolone, our patient continued to have fever, diarrhoea and worsening transaminitis. Hence, intravenous hydrocortisone was given instead. The patient responded positively with rapid resolution of fever and diarrhoea episodes, negating the need for endoscopic examinations. Her skin condition improved, with decreasing erythema and superficial desquamation. The liver enzymes normalised and the persistent hypokalaemia resolved with cessation of diarrhoea and improved oral intake. Upon discharge, the patient was given a week's supply of oral prednisolone, which was to be slowly tapered off over the course of a few weeks. However, she defaulted on further reviews. A telephone call to her confirmed that her rashes resolved after a month with post-inflammatory hyperpigmentation.

DISCUSSION

The pathogenesis of DHS remains unclear. Over 50 drugs have been pinpointed to be the culprits, and among them the most notorious are the anticonvulsants.⁽⁵⁾ Amoxicillin-clavulanic acid, the culprit drug in our patient, was previously identified as a definite cause of DHS.⁽⁵⁾ It has been postulated that DHS occurs upon a favourable combination of the patient's genetic predisposition and sufficient exposure to the culprit drug.⁽⁶⁾

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Human leucocyte antigen-related genes have been identified as predictors of certain severe cutaneous adverse drug reactions, for example, HLA-B*5801 is associated with allopurinol-induced DHS among the Han Chinese.⁽⁷⁾ Although the exact link is still unclear, reactivation of the HHV-6 and HHV-7 has been associated with DHS.

The diagnosis of DHS is challenging due to its broad spectrum of clinical features and long latency. Multiple sets of diagnostic criteria have been proposed, including that by the RegiSCAR study group.⁽⁴⁾ Patients with a drug rash must fulfill at least three out of four systemic features, which consist of fever, lymphadenopathy and haematological abnormalities or internal organ involvement.⁽⁴⁾ High fever (> 38°C), haematological derangements of leucocytosis with eosinophilia, and hepatitis with either hepatocellular or cholestatic abnormalities are the more common features.⁽⁸⁾ Skin lesions are prominent, and often urticated and maculopapular. In a retrospective study of 27 Singaporean patients, 81.5% of them had a morbilliform eruption with typical histology of superficial perivascular dermatitis. There was no association between the culprit drug and the morphology of the rash. Mucositis and facial oedema may also be present.^(5,8) The skin eruptions may be dramatic and extensive, but systemic involvement results in greater morbidity. Other internal organs such as the kidneys, lungs and heart may also be involved. The mortality rate from DHS is around 10%, with fulminating liver failure as the main contributor.^(4,9)

Nonspecific gastrointestinal symptoms often occur in DHS, but are rarely investigated, and probably underreported. This might mean an underestimated prevalence of gastrointestinal tract involvement in DHS.⁽³⁾ Few cases of oesophagitis and colitis with diarrhoea in DHS have been published, with one case detailing fatal massive intestinal haemorrhage. This fatal case had endoscopic biopsies of circumferential erosive oesophagitis and ulcerative colitis with complete mucosal destruction. Histology of the colon revealed a diffuse inflammatory lymphocytic infiltrate without granuloma, eosinophils or viral inclusions.⁽³⁾ Similar colonoscopy and histological findings have also been reported in a North African woman with DHS.⁽³⁾

It is paramount to exclude infectious and inflammatory causes of colitis. As we were exploring these differential diagnoses, our patient improved significantly upon the introduction of intravenous

steroids. We postulate that hypermotility of her gut resulted in poor absorption of oral corticosteroids. Thus, only when intravenous hydrocortisone was initiated did the clinical features of fever, diarrhoea with hypokalaemia and transaminitis resolve.

Currently, DHS is first managed by identifying and withdrawing the culprit drug. Moderate to high doses of oral corticosteroids are required, with slow tapering over the following months to prevent relapse. Other immunosuppressive agents such as cyclosporine are sometimes required.⁽¹⁰⁾ When the gastrointestinal system is involved, with possible accelerated gut motility and mucosal damage affecting the absorption of oral prednisolone, intravenous corticosteroids should be considered. Supportive treatment with the monitoring of fluid and electrolyte statuses, and judicious replacement is fundamental in the management of DHS patients with gut involvement. When severe gastrointestinal involvement appears in the course of DHS, endoscopic investigations should also be considered in order to exclude other causes such as infections and to evaluate the extent of mucosal damage so as to further aid treatment.

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