Mononucleosis-Like Drug Rash: An Interesting Case Presentation

Reshma T. Vishnani, Ram H. Malkani, Afsha A. Topal, H. G. Desai

Departments of Dermatology, Gastroenterology, Jaslok Hospital and Research Centre, Mumbai, Maharashtra, India

Abstract
Dapsone hypersensitivity syndrome (DHS) is a rare adverse effect of the commonly prescribed drug dapsone. We present a case of a 35-year-old male who was referred to us from the gastroenterologist with complaints of rash, nausea, vomiting, and jaundice since 2 days with a provisional differential diagnosis of infectious mononucleosis or viral exanthema. On enquiry patient gave history of taking dapsone a week prior for refractory urticaria. After thorough investigations we diagnosed him with DHS. This syndrome occurs in a relatively small proportion of patients, but it is associated with considerable morbidity and mortality. The reason for presenting this case is to remind physicians of the unpredictability and potential severity of this reaction which makes it a major concern in clinical practice.

Keywords: Dapsone, dapsone hypersensitivity syndrome, dapsone hypersensitivity syndrome, mononucleosis-like drug rash

Introduction
Dapsone is a potent anti-inflammatory and antiparasitic compound with a variety of adverse effects, including hemolytic anemia, methemoglobinemia, hepatic involvement (hepatocellular or cholestatic disease, or both), cutaneous involvement (exanthematous eruption, Steven-Johnson syndrome, or toxic epidermal necrolysis), agranulocytosis, nephritis, pneumonitis, hypothyroidism, and the potentially fatal DHS. DHS is a known but rare idiosyncratic multiorgan syndrome which was first reported in as early as 1950 by Lowe and was termed as dapsone syndrome by Allday and Barnes in 1951. The incidence of DHS ranges from 0.5 to 3%. It typically presents with a triad of fever, skin eruption, and internal organ (lung, liver, neurological, and other system) involvement, occurring several weeks to as late as 6 months after the initial administration of drug.

We present an interesting case of a 35-year-old male patient with DHS in whom the clinical presentation mimicked an infectious mononucleosis-like viral exanthema.

Case Report
A 35-year-old male was referred to us from the gastroenterologist for minimally itchy red rash all over the body along with swelling over the face since 2 days. He also had moderate continuous fever, sore throat, weakness, jaundice, nausea, and vomiting since 1 day. The patient was icteric, had hepatosplenomegaly and generalized lymphadenopathy (bilateral cervical, preauricular, submandibular, retroauricular, axillary and inguinal). Cutaneous examination revealed generalized erythematosus maculopapular rash with acral and facial edema. On further enquiry, we found that the patient had been on treatment for refractory urticaria with dapsone in a dose of 100 mg/day; this medication was started a week before the appearance of symptoms. In view of his history and clinical features, a provisional diagnosis of DHS, infectious mononucleosis, and leukemia were considered.

Pertinent laboratory investigations revealed a hemoglobin of 10.9 gm/dl, an elevated total white cell count of 16,270/mm³ with 10% eosinophils, along with elevated levels of serum bilirubin (total: 6 mg/dl; direct: 3.6 mg/dl) and liver enzymes [aspartate transaminase (AST): 495; alanine transaminase (ALT): 768; gamma-glutamyltransferase (GGT): 179; alkaline phosphatase (ALP): 247]. Urine examination showed...
presence of bile salts, bile pigments, and granular casts. Heterophile antibody test done immediately, and repeated at 1 and 2 weeks were persistently negative, thus ruling out infectious mononucleosis. Patient did not have glucose-6-phosphate dehydrogenase deficiency (G6PD). Computerized tomography (CT) scan (chest and abdomen) showed multiple enlarged nonnecrotic lymph nodes in the neck, axilla, and inguinal regions; right pleural effusion with basal atelectasis; and mild hepatosplenomegaly. Skin biopsy showed mild spongiosis, focal parakeratosis and interface changes with moderately dense, superficial perivascular infiltrate of lymphocytes, histiocytes, and occasional eosinophils. Occasional necrotic keratinocytes were also seen, consistent with maculopapular drug eruption. No evidence of leukemic cells infiltration in the dermis or subcutaneous tissue. In view of the clinical and laboratory findings, a final diagnosis of DHS was made. Dapsone was discontinued and the patient was started on tablet prednisolone 40 mg/day along with supportive therapy; the dose of prednisolone was tapered slowly over a period of 6 weeks. The patient responded well to therapy; 10 days following the start of therapy his rash had considerably reduced and fever subsided, and over a period of 4 weeks his serology values were within normal limits.

**Discussion**

Dapsone is a widely used drug because of its antibiotic and anti-inflammatory effects, which is mainly related to its interference with neutrophil chemotactic migration and adherence. Dapsone, after absorption from the gastrointestinal tract, is metabolized in the liver and excreted by the kidneys. It has a long elimination half-life (about 24-36 h). Thus, the adverse reactions may appear after a long metabolite period; in our case, the reaction was seen after 1 week. Though, the exact immune mechanism causing DHS is not clear, some mechanisms proposed are: DHS might be a combination of type I, type IV, and perhaps type III Gel and Coombs hypersensitivity reactions or it could be a modified graft versus host disease mediated by activated T-lymphocytes. Prussick and Shear have suggested that there is some evidence suggesting that the metabolic differences in the production and detoxification of reactive metabolites are an important factor in sulfonamide hypersensitivity reactions.

Richardus and Smith have outlined the following criteria for diagnosis of DHS: (a) Symptoms manifesting within 8 weeks of starting therapy and resolving after withdrawal of the drug; (b) symptoms not attributable to any other drug used simultaneously; (c) symptoms not attributable to lepra reaction; (d) no other disease liable to cause similar symptoms is diagnosed, and (e) two of the following signs and symptoms are present: Fever, skin eruption, lymphadenopathy, liver pathology (hepatomegaly, jaundice, and/or abnormal liver function tests (LFTs)). These criteria were met in our patient. Though unlike other drug hypersensitivity syndromes, eosinophilia is usually absent in DHS. Our patient did show eosinophilia. Thus, our case of DHS may potentially be considered a variant of DRESS syndrome (drug reaction with eosinophilia and systemic symptoms). Furthermore, slow acetylators may be associated with an increased risk of development of this syndrome. Prompt withdrawal of dapsone, initiation of systemic glucocorticoids (1 mg/kg/day prednisolone tapered over 5-6 weeks), supportive measures and minimal use of other drugs are essential in the management of DHS. For patients with dapsone-induced hemolysis, vitamin E supplementation might be beneficial while in patients with methemoglobinemia coadministration of cimetidine can have an ameliorative effect. These were not required in our case. Rechallenge with dapsone can be performed but is not recommended due to potential hazards associated with it. An important issue to remember in the management is that patients with DHS are at a higher risk of development of hypothyroidism after 3 months, suggesting the need to repeat thyroid function tests at 3 monthly intervals, our patient was tested for the same and his result was within normal limits. The etiology attributed seems linked to the presence of autoantibodies, including antimicrosomal antibodies. This hypersensitivity reaction appears in patients who are generally unable to detoxify reactive metabolites produced by thyroid peroxidase. Since genetic factors have been implicated in the pathogenesis of DHS, we made the relatives aware of this syndrome and their enhanced risk of developing similar adverse reaction should they take dapsone.

**Conclusion**

The focus of this presentation is to create awareness and vigilance towards the well-known but rare complication of the widely used drug dapsone (even in non-leprosy use), which closely mimics infectious mononucleosis-like syndrome and has significant morbidity and mortality associated with it.

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