

Liver injury, rash, and encephalopathy in a 23-year-old Asian man prescribed dapsone

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Clinical Implications

- Dapsone hypersensitivity syndrome (DHS) is a potentially life-threatening side effect of dapsone. Clinicians should be aware of predisposing factors and symptoms of DHS for swift diagnosis and management.

TO THE EDITOR:

Dapsone is used to treat multiple conditions, including leprosy. A rare and potentially fatal effect of dapsone use is dapsone hypersensitivity syndrome (DHS), which typically presents with fever, rash, and internal organ involvement.

A 23-year-old Asian man in Southern California reported a “spider bite” and completed a 20-day prescription of 100 mg dapsone daily. One week after finishing the prescription, he developed abdominal pain and vomiting. He was admitted to an outside hospital with concern for cholecystitis and then developed an itchy rash on his distal extremities and a 103°F fever. Antibiotics were started; however, the patient developed insomnia and delusions. After 1 week, the patient was transferred to our hospital.

On arriving, the patient had a temperature of 98°F, blood pressure of 88/75 mm Hg, pulse of 125 beats/minute, and respiratory rate of 25 breaths/minute. Physical examination was significant for scleral icterus, oral mucosal sloughing, lymphadenopathy, and an erythematous nonblanching morbilliform rash that involved 100% of the patient’s body. Initial labs (Table I) were notable for white blood cell (WBC) 35.1, eosinophils 1%, atypical lymphocytes 3%, blood urea nitrogen (BUN) 38, creatinine (Cr) 1.7, alanine aminotransferase (ALT) 1576, aspartate aminotransferase (AST) 1699, direct bilirubin 8.8, indirect bilirubin 2.3, total bilirubin 11.1, prothrombin time (PT) 23.2, international normalized ratio (INR) 2.1, and partial thromboplastin time (PTT) 45. Shortly after presentation, he developed an acute confusional state, requiring sedation and intubation for acute encephalopathy.

Given the patient’s history of dapsone use, DHS was suspected. The patient was immediately started on 40 mg intravenous (IV) dexamethasone every 8 hours. In addition, he received 1 course of plasmapheresis and 4 days of 30 g intravenous immunoglobulin (IVIG) daily (0.5 g/kg). Continuous renal replacement therapy (CRRT), controlled pressure hemofiltration used in hemodynamically unstable renal failure patients, was also initiated for renal failure.¹

On day 5 after transfer, human herpesvirus 6 (HHV-6) blood polymerase chain reaction (PCR) returned positive. Additional infectious workup was negative, including blood, urine, and skin cultures; mycoplasma; coccidioidomycosis; coxsackie; measles; parvovirus; Rocky Mountain spotted fever; rubella; West Nile virus; viral hepatitis; HIV; cytomegalovirus; leptospirosis; chikungunya; adenovirus; Epstein-Barr virus; and parvovirus. Glucose-6-phosphate dehydrogenase activity was normal. Abdominal wall skin punch biopsy revealed interface dermatitis and a vacuolar pattern with subepidermal clefting and purpura, consistent with DHS.

The patient’s clinical condition improved and on day 6 after transfer, he was extubated, CRRT was stopped, and renally dosed ganciclovir was initiated (200 mg [~ 5 mg/kg every 12 hours] then 170 mg [~ 2.5 mg/kg every 12 hours]). IV dexamethasone was transitioned to 62 mg oral prednisone twice per day with subsequent taper over the course of his hospital stay (Table II).

On discharge, the patient’s rash and labs had improved (Table I). HHV-6 PCR copies were no longer detected. On day 15 after transfer, the patient was discharged home with 30 mg oral prednisone twice per day (Table II) with follow-up in dermatology clinic. The patient’s rash resolved 15 days after discharge.

The incidence of DHS ranges from 0.5% to 3% and affects males and females in a 2.2:1 ratio.^{2,3} The average age of affected individuals is 32.3 with an average latent period of 30 days after taking dapsone. DHS prevalence among Chinese patients is 1.5% with a fatality rate of 9.6%.⁴ DHS is considered a variant of drug reaction with eosinophilia and systemic symptoms (DRESS).⁵

DHS is a clinical diagnosis, as there are no confirmatory laboratory tests. Eosinophilia is only found in 15.4% of patients with DHS.² Skin rash involvement $>30\%$ of body surface area is associated with poor outcome. DHS should be suspected and diagnosed in the setting of symptoms within 2 to 8 weeks of dapsone exposure.⁴ However, DHS is dose independent and can still manifest up to 6 months after treatment initiation.⁵

Hypersensitivity to dapsone appears to be associated with a patient’s immune status.⁶ The pathogenesis of DHS may be due to formation of dapsone haptens, leading to production of inflammatory cytokines and antidapsone antibodies. Affected patients tend to be younger, suggesting decreased enzyme metabolism and toxic metabolite production with aging.² Although our patient’s HLA status remains unknown, in patients with leprosy, *HLA-B*13:01* is a risk factor for DHS (odds ratio of 20.53) and is present in 2% to 20% of Chinese individuals.⁷

Furthermore, HHV-6 reactivation, commonly seen in younger patients via dapsone-induced immunosuppression, is a diagnostic criterion for drug-induced hypersensitivity syndrome by the Japanese consensus group and is a key component in the pathogenesis of DRESS.⁸ HHV-6 reactivation in drug hypersensitivity is correlated with worsening symptoms and disease course.⁹ Decreasing steroid dosage during treatment can be associated with flares, as the body’s immune function recovers and mounts a new response against the virus. In the case presented, starting ganciclovir had a beneficial outcome; however,

TABLE I. Initial and discharge laboratory values

Laboratory test	Reference range	Initial	Discharge
WBC	(4-11 1000/ μ L)	35.1	11.9
Eosinophil (%)	N/A	1	0
Atypical lymphocyte (%)	N/A	3	1
BUN	(5-25 mg/dL)	38	30
Cr	(0.8-1.3 mg/dL)	1.7	1.5
ALT	(0-45 units/L)	1576	229
AST	(0-35 units/L)	1699	41
Direct bilirubin	(<0.4 mg/dL)	8.8	1.3
Indirect bilirubin	(<1 mg/dL)	2.3	1.1
Total bilirubin	(0.1-1.2 mg/dL)	11.1	2.4
PT	(0-11.5 s)	23.2	15.8
PTT	(22-34 s)	45	N/A
INR	(0.9-1.1)	2.1	1.3

ALT, Alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Cr, creatinine; INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time; WBC, white blood count.

TABLE II. Steroid taper

Steroid	Dose	Day
Dexamethasone	40 mg every 8 h	1-3*
Dexamethasone	30 mg every 8 h	4-7
Dexamethasone	30 mg every 12 h	8-10
Prednisone	62 mg twice a day	11-12
Prednisone	30 mg twice a day	13-16†
Prednisone	20 mg twice a day	17-18
Prednisone	15 mg twice a day	19-22
Prednisone	10 mg twice a day	23-24
Prednisone	5 mg twice a day	25-29

*Transferred from outside hospital on day 1.

†Discharged on day 15.

future research remains to be conducted on the use of antiviral drugs in the setting of HHV-6 positive DHS.⁸

Current treatment for DHS includes high-dose steroids (equivalent to oral prednisolone 1-2 mg/kg/day) until resolution of symptoms.² IVIG and plasma exchange have also been successfully implemented in case studies of DRESS refractory to steroids alone.¹⁰ Skin lesion progression halts in an average of 5 days and subsides in an average of 18 days. Recovery takes an average of 28 days and normalization of lab values occurs in 6 to 10 weeks. Dapsone can last up to 35 days in the body and a steroid taper over 4 to 6 weeks is recommended.² In addition, thyroid stimulating hormone should be checked 3 months after diagnosis to evaluate thyroid function.³ Some studies have

attempted dapsone challenges after DHS recovery; however, this is not recommended as rechallenge with dapsone can be hazardous.⁶

In summary, dapsone continues to be commonly used and providers should be familiar with diagnosing and managing DHS. The mortality of DHS is as high as 12% to 23%.⁵ Certain phenotypes, ethnicity, and HHV-6 positivity may help guide diagnosis and prognosis. High suspicion based on relevant history and presentation is crucial in identifying DHS, discontinuing dapsone, and initiating high-dose steroids.

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No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication May 6, 2018; revised July 11, 2018; accepted for publication July 18, 2018.

Available online August 24, 2018.

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2213-2198

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<https://doi.org/10.1016/j.jaip.2018.07.040>

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