Hepatic injury in Sulfone Syndrome: Hepatitis or Cholestasis?

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Abstract

A patient with cholestatic jaundice associated with other features of dapsone-induced sulfone syndrome is described and relevant literature reviewed.


Key Words: Dapsone, drug hepatotoxicity

Dapsone can rarely cause a hypersensitivity reaction called 'sulfone syndrome', consisting of fever, hepatitis, exfoliative dermatitis, lymphadenopathy, methemoglobinemia and hemolytic anemia. We report a patient with sulfone syndrome in whom liver histology was suggestive of a predominantly cholestatic injury.

A 23-year-old man presented with fever and jaundice of 10 days duration while on dapsone (100 mg/day), clofazimine (100 mg/day) and rifampicin (600 mg once a month) for 1 year for suspected pulmonary leprosy. There was no pruritus or clay colored stools. Though he discontinued these drugs on the sixth day of the fever, he developed a generalized non-pruritic, macular rash, cervical lymphadenopathy and hepatosplenomegaly. Examination revealed jaundice, generalized erythematous macular rash, cervical lymphadenopathy and hepatosplenomegaly. There were no cutaneous lesions of leprosy or peripheral nerve thickening. Laboratory data on admission included: HB 10 g/dL; total leucocyte count 18,900/μL (polymorphs 55%, lymphocytes 35%, eosinophils 10%) and ESR 125 mm/hr. Peripheral blood smear revealed polychromatoblasts, anisocytosis, target cells and a corrected reticulocyte count of 4.6%. Liver function tests were as follows: total bilirubin 6.8 mg/dL (direct 3.5); AST 129 IU/L; serum ALT 187 IU/L and alkaline phosphatase (AP) 376 IU/L. Blood and urine cultures were sterile. Paul-Bunnell test and HbA1c were negative and glucose 6-phosphatase dehydrogenase level was normal.

The patient was managed with anti-pyretics and antihistamines. The fever declined after 48 h and disappeared on the 5th day. The macular rash was replaced by marked exfoliative dermatitis after 7 days. No fresh lesion appeared thereafter. A liver biopsy showed maintained lobular architecture with mixed inflammatory cells including eosinophils and histiocytes (Fig), focal cellular and consolitary cholestasis. Subsequent recovery was unremarkable. Serial follow up showed complete biochemical recovery over 6 weeks. Subsequently, a cutaneous nerve biopsy confirmed the diagnosis of peripheral neuropathy which was treated with rifampicin and clofazimine without any untoward reaction.

Sulfone syndrome is a rare complication of dapsone therapy with a frequency of 0.2%-0.5%. Although presence of hepatic involvement in this syndrome is well described,6-8 its biochemical and histological pattern has not been adequately characterized.

Fig. Liver biopsy showing widening of portal tracts by mixed inflammatory cells and histiocytes (H & E, 200 x)

Recently, criteria have been laid down for drug induced liver injury based on R value (calculated as the ratio of serum activity of ALT/serum activity of AP, each being expressed as a multiple of upper limit normal, both being measured simultaneously). R value > 5 is suggestive of hepatocellular injury and that < 2 of cholestatic injury, whereas an intermediate value suggests a mixed pattern.4 A critical analysis of previously described cases applying these criteria shows cholestasis to be the commonest pattern of injury. Hence use of the term 'hepatitis' to denote liver involvement in the sulfone syndrome without biochemical and histological characterization is inappropriate as has been done previously.4,8

Most patients respond well to withdrawal of the drug with only a few requiring corticosteroid administration.5 Rechallenge with dapsone may prove dangerous.

References