Submassive Hepatic Necrosis in a Patient with AIDS

by Mujtaba I. Butt, Kidada Gilbert-Lewis, Cherif El-Younis, Nora V. Bergasa

The prevalence of drug-induced hepatitis is associated with substantial morbidity; its recognition is crucial in the management as the culprit agent can be discontinued. We report a case of drug-induced hepatitis.

CASE PRESENTATION

A 43-year-old man presented to the Emergency Department with fever, chills and a generalized rash of two weeks duration that began on his chest and back. The patient reported chronic non-productive cough and shortness of breath with new symptoms of generalized fatigue, malaise and a 20 pound weight loss over one month. Complete blood count revealed marked eosinophilia. The patient was prescribed diphenhydramine and steroid cream in ED for presumed viral exanthem.

The patient had AIDS for eight years with a CD4 count of 210 cell/mm³, chronic hepatitis C infection and previous hepatitis B infection with liver biopsy showing hepatitis. He had a positive purified protein derivative test and had been treated with isoniazid five years prior to admission. The patient had a history of cocaine and alcohol abuse in the past and history of smoking.

The patient had been taking nelfinavir, zidovudine and lamivudine for his HIV infection for five years. Three months prior to admission the patient was started on dapsone for *pneumocystis carinii pneumonia* (PCP) prophylaxis as sulfamethoxazole/trimethoprim had been associated with hepatitis.

PHYSICAL EXAMINATION

The patient’s physical examination was notable for a diffuse scaly rash with lichenification, eczematous changes, bilateral ulceration at the base of the neck, ante-cubital fossae and groin area. Oral mucosa revealed erythema with whitish plaques suggestive of candidiasis. He had a left axillary lymph node, 1 × 1 cm, firm and non-tender. His abdomen was soft, non-tender with no hepatosplenomegaly, ascites or asterixis. The rest of the physical examination was unrevealing.

Laboratory findings on admission are shown in Table 1.

HOSPITAL COURSE

The patient was admitted to the hospital with a presumed diagnosis of adverse drug reaction to dapsone. All potential hepatotoxic medications, including dapsone, were stopped. His hemoglobin level decreased in association with increase serum activity of lactate dehydrogenase and low haptoglobin serum levels suggesting hemolysis.

Activity of serum transaminases continued to increase along with bilirubin (Table 2) and coagulation profile was further altered. An adverse drug reaction to dapsone was considered to be the most likely diagnosis; however, due to continued worsening of liver function and coagulation profile a diagnosis of autoimmune hepatitis was entertained.

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Table 1
Laboratory Findings on Admission

<table>
<thead>
<tr>
<th>Test</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>8.6 g/dl</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>26.7%</td>
</tr>
<tr>
<td>Platelets</td>
<td>417 cells/mm³</td>
</tr>
<tr>
<td>WBC</td>
<td>10.5 cells/mm³</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>65.3%</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>27.5%</td>
</tr>
<tr>
<td>Monocytes</td>
<td>7.0%</td>
</tr>
<tr>
<td>Basophils</td>
<td>0.2%</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>0.3%</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>18.4 secs</td>
</tr>
<tr>
<td>Thromboplastin time</td>
<td>57.3 secs</td>
</tr>
<tr>
<td>Sodium</td>
<td>131 mEq/l</td>
</tr>
<tr>
<td>Potassium</td>
<td>4.3 mEq/l</td>
</tr>
<tr>
<td>Chloride</td>
<td>102 mEq/l</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>24 mEq/l</td>
</tr>
<tr>
<td>Urea nitrogen</td>
<td>15 mg/dl</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.8 mg/dl</td>
</tr>
<tr>
<td>Glucose</td>
<td>112 mg/dl</td>
</tr>
<tr>
<td>Calcium</td>
<td>8.2 mg/dl</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>165 U/L</td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td>388 U/L</td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>274 U/L</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>3.7 mg/dl</td>
</tr>
<tr>
<td>Direct bilirubin</td>
<td>2.9 mg/dl</td>
</tr>
<tr>
<td>Lactate Dehydrogenase</td>
<td>817 u/L</td>
</tr>
</tbody>
</table>

Figure 1. Biopsy specimen of the liver.
Panels A and B (hematoxylin and eosinophil staining at 20 and 40×, respectively) showed a background of chronic hepatitis with superimposed multicellular hepatic necrosis (arrow).
Panel C (hematoxylin and eosinophil staining at 20×) showed large areas of collapse with loss of hepatic parenchyma and bile ductular proliferation, consistent with regeneration (arrow).
Panel D (reticulin staining at 20×) showed necrosis without significant fibrosis as suggested by the absence of reticulin staining (arrow).
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Additional laboratory tests were ordered as shown in Table 3.

A transjugular liver biopsy was performed in an effort to improve the accuracy of diagnosis. Liver biopsy showed superimposed confluent hepatic necrosis on the background of chronic hepatitis, along with large areas of collapse with loss of hepatic parenchyma and bile ductular proliferation without significant fibrosis (Figure 1).

The patient was started on prednisone 60 mg and his clinical condition and liver function improved. He was discharged home on tapering doses of prednisone and on follow-up visits his liver function tests returned to his baseline values.

DISCUSSION

The patient described in this report had exfoliative dermatitis, axillary lymphadenopathy, fever, hemolytic anemia, hepatitis, hyperbilirubinemia, and hypoaalbuminemia. Liver biopsy showed confluent hepatic necrosis on a background of chronic hepatitis, consistent with the patient’s chronic hepatitis C infection. The acute features in this patient were suggestive of an adverse reaction to dapsone known as “Dapsone Syndrome.”

The dapsone syndrome was first described by Lowe and Smith (1) in 1949, when they noted exfoliative dermatitis in patients treated with dapsone for leprosy. Since then, the term has been expanded to include hemolytic anemia, hepatitis, fever, lymphadenopathy and atypical lymphocytosis. A review by Mohle-Boetani (2,4) found that it occurs in 0.2%–0.5% of patients on dapsone therapy at doses between 50–200 mg daily for an average of two months (range of one-to-32 weeks) of therapy.

Dapsone (4,4'-diaminodiphenylsulfone) is the parent compound of the sulfones. It has been the drug of choice for the treatment of leprosy (3), dermatologic conditions including dermatitis herpetiformis and for the prevention and treatment of Pneumocystis carinii pneumonia (PCP) infection in patients with AIDS.

Adverse effects of dapsone are either pharmacologic or idiosyncratic. The dapsone syndrome, agranulocytosis and peripheral neuropathy are idiosyncratic (5,16). Pharmacological effects include methemoglobinemia, hepatitis, cholestasis, and leukopenia. The constellation of features included in this syndrome are fever, exfoliative dermatitis, lymphadenopathy, lymphocytosis, methemoglobinemia, hemolytic anemia and hepatotoxicity. It may appear in an incomplete form as hepatitis (6) or exfoliative dermatitis.

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The dapsone syndrome can be considered a manifestation of the drug rash with eosinophilia and systemic symptoms known as “DRESS syndrome,” which is a serious condition that has been reported in association with various drugs, including sulfonamides, minocycline, anticonvulsants, and gold salts (8).

The hyperbilirubinemia of dapsone syndrome can occur either due to hepatotoxicity alone or its combination with hemolysis. Both hepatocellular and cholestatic injuries have been described in the dapsone syndrome (9). Also, severe cholangitis has been described in a case report as a part of dapsone syndrome (7). Hepatocellular injury is characterized on liver histology by predominantly an eosinophilic lobular and portal infiltrate and elevated activity of transaminases. Hepatitis may lead to liver failure and death (10,11,13). When associated with a cholestatic pattern the course is less severe.

The mechanism of injury is most likely a hypersensitivity reaction (6,12,14,17). Although, anecdotal reports have showed good response with corticosteroid therapy (15–17) in severe cases, these results have not been validated by controlled studies. Cytochrome P-450 induced metabolism of dapsone to hydroxylamines is responsible for the hematologic toxicity of dapsone, which include methemoglobinemia, hemolysis and agranulocytosis. Hydroxylamines exposed erythrocytes reach bone marrow where they release hydroxylamines in sufficient concentration to kill the granulocyte precursor leading to agranulocytosis (18).

The incidence of dapsone syndrome is increasing especially due to increased use for prophylaxis against PCP in HIV/AIDS patients. There have been case reports of dapsone syndrome associated with hepatitis B and hepatitis E infection (19). As an analogy, HCV infection may be a risk factor for development of dapsone syndrome. Dapsone syndrome has resulted in lethal hepatic failure in an HIV infected patient as outlined in a case report in 1994 (20).

It is reported that patients with hepatitis C and HIV co-infection are at increased risk of rapidly progressive liver disease (21). Co-infection with these two viruses may also contribute to an increased vulnerability for development of the dapsone syndrome.

In summary, our case exhibited many of the key features of the dapsone syndrome including exfoliative dermatitis, fever, hemolytic anemia, and hepatitis as evidenced by liver biopsy and improvement in the patient’s condition after discontinuation of dapsone.

It is emphasized that dapsone syndrome causes significant morbidity and although rarely, mortality. Accordingly, early recognition of this complication is necessary for prompt discontinuation of this drug.

References