Cholestasis secondary to Hodgkin’s disease: report of 2 cases of vanishing bile duct syndrome

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ABSTRACT

Only a small percentage of patients with Hodgkin’s disease become clinically jaundiced during their disease. This jaundice may be secondary to biliary obstruction, hemolysis, direct hepatic infiltration by the disease, drug toxicity or viral hepatitis. Vanishing bile duct syndrome secondary to Hodgkin’s disease is a rare cause of cholestasis in these patients, only 13 cases having been reported so far. The authors describe 2 patients who developed severe jaundice secondary to Hodgkin’s disease due to vanishing bile duct syndrome affecting small intrahepatic bile ducts.

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Key words: Hodgkin’s disease, vanishing bile duct syndrome, cholestasis, ursodeoxycholic acid

Hepatic involvement is quite common among patients with Hodgkin’s disease (HD), accounting for as many as 50% of the findings in post mortem examinations. However, only 3 to 13% of these patients become clinically jaundiced. Several factors have been implicated as causes of cholestasis in HD, including biliary obstruction, due either to enlarged hilar lymph nodes or to primary involvement of the common bile duct, direct hepatic infiltration by the lymphoma, drug toxicity, hemolysis or viral hepatitis. The reports of vanishing bile duct syndrome (VBDS) associated with HD in the literature do not exceed 13 cases. The authors present 2 patients who developed severe jaundice due to VBDS affecting small intrahepatic bile ducts secondary to HD.

Case reports

Case #1

A 27-year-old woman presented with a 4 month history of jaundice and severe pruritus, associated with fever and 14 kg of weight loss. She had no previous history of alcohol or drug use, or any liver disease. At physical examination, widespread lymphadenopathy and hepatosplenomegaly were found. Investigations on admission showed a pattern of biochemical values that was consistent with cholestasis and hepatocellular injury (Table 1). Serologic tests for hepatitis A, B and C and cytomegalovirus were all negative, as were those for antimitochondrial antibodies. Imaging studies demonstrated an enlarged mediastinal mass and retroperitoneal lymphadenopathy without signs of biliary obstruction. A lymph node biopsy showed HD of mixed cellularity type. The patient was treated with 6 cycles of the MOPP chemotherapy regimen and gained complete remission except for the persistent cholestasis and worsening of the liver function tests. Exhaustive investigations showed no evidence of abdominal lymphadenopathy or biliary obstruction. A liver biopsy was carried out showing intrahepatic cholestasis associated with severe ductopenia and pericentral fibrosis (Figure 1), but no histological evidence of infiltration by HD.

Case #2

A 50-year-old woman presented with a 3 month history of cervical lymphadenopathy associated with 11 kg of weight loss and night sweats. A chest X-ray on admission demonstrated an enlarged mediastinal mass and an abdominal ultrasound showed enlargement of abdominal lymph nodes. A cervical lymph node biopsy demonstrated HD of nodular sclerosing type. The patient was treated with 5 cycles of the...
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MOPP/ABV chemotherapy regimen. Eight months later the patient became cholestatic presenting with severe refractory jaundice and pruritus. Investigations demonstrated biochemical values consistent with hepatocellular injury and cholestasis (Table 2). There were no antimitochondrial antibodies, no evidence of persistent abdominal lymphadenopathy or signs of biliary obstruction. A liver biopsy was carried out showing intrahepatic cholestasis and the diagnosis of primary biliary cirrhosis due to idiopathic intrahepatic ductopenia. The patient had a liver transplant but eventually died on the 39th day after transplantation due to septic shock. The autopsy studies did not reveal any evidence of hepatic HD in this patient.

Discussion
VBDS, the syndrome of disappearing intrahepatic bile ducts has been described as occurring secondary to several developmental, immunologic, infective, vascular or chemical phenomena. The immunologic group of etiologies includes liver allograft rejection, severe acute or chronic hepatic graft-versus-host disease, primary biliary cirrhosis and, possibly, HD.4,7 The syndrome is characterized by loss of the interlobular bile ducts in more than 50 percent of the portal tracts and is suspected when other known causes associated with a reduction in the number of bile ducts have been excluded.

Several explanations have been proposed for the association between HD and VBDS, the most likely one being the release of toxic cytokines from lymphoma cells. These could cause bile duct damage directly or result in the recruitment of other effector cells, which in their turn lead to bile duct destruction. Such a mechanism might account for the disparity between the relatively minor load of lymphomatous disease and the very severe cholestasis observed in some patients.4,10 Both of our patients presented with cytokine release-related symptoms of HD.

If such a mechanism is really the main explanation for the cholestatic lesions found in these patients, how can one explain the fact that not all patients with HD develop, at least, some degree of idiopathic intrahepatic cholestasis? A rational explanation could be based on the findings of Moreno et al.,11 who described 24 asymptomatic patients with moderate impairment of liver function of unknown cause, whose liver biopsies showed benign mild ductopenia. Patients like these, once affected by HD, could be predisposed to developing a more severe form of biliary ductopenia, which has been described as VBDS.

According to recent reports, several patients have benefited from ursodeoxycholic acid (UDCA) treatment of cholestatic diseases. Significant improvement in liver function tests occurred in four of five asymptomatic patients with the benign form of biliary ductopenia;11 there was an improved survival rate and decreased need for transplantation in primary biliary cirrhosis patients;12,13 liver function gradually normalized and the bile ducts reappeared without cholestatic damage in hepatic GvHD after bone marrow transplantation.14 Based on these findings, we may assume that the introduction of UDCA concomitant to chemotherapy for HD patients with VBDS may be a very important factor delaying progression into liver cirrhosis.

In conclusion, special attention should be paid to abnormal liver function tests with no clear signs of liver compromise by HD prior to chemotherapy. These findings, which are very often interpreted as disseminated (stage IV) disease, may sometimes predict the development of VBDS, which could, in some cases, be attenuated by UDCA therapy.

Table 2. Biochemical values of patient #2 eight months after chemotherapy.

<table>
<thead>
<tr>
<th></th>
<th>DB</th>
<th>TB</th>
<th>AST</th>
<th>ALT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>16.3</td>
<td>21.7</td>
<td>78</td>
<td>48</td>
</tr>
<tr>
<td>1 month</td>
<td>18.7</td>
<td>23.1</td>
<td>93</td>
<td>52</td>
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<tr>
<td>3 months</td>
<td>20.4</td>
<td>25.6</td>
<td>95</td>
<td>53</td>
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<tr>
<td>5 months</td>
<td>20.8</td>
<td>25.2</td>
<td>102</td>
<td>49</td>
</tr>
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Abbreviations: DB: direct bilirubin; TB: total bilirubin; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

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References