CASE REPORT

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Vanishing bile duct syndrome: A rare cause of jaundice in Hodgkin's lymphoma

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Vanishing bile duct syndrome refers to a group of disorders which are characterized by prolonged cholestasis as a consequence of progressive destruction and disappearance of intrahepatic bile ducts. We present a case of Hodgkin's lymphoma presenting with vanishing bile duct syndrome. Liver damage is relatively common in Hodgkin's lymphoma. But only a small percentage of these patients develop jaundice. This may be secondary to drug toxicity, hemolysis, direct invasion by malignant cells or by extensive, obstructive lymphadenopathy. Vanishing bile duct syndrome secondary to Hodgkin's lymphoma is a rare cause of cholestasis in these patients. The mechanism of vanishing bile duct syndrome in Hodgkin's lymphoma is poorly explained, but a paraneoplastic effect seems most likely.

Key words: Vanishing bile duct syndrome, Hodgkin's lymphoma, cholestasis

Yok olan safra kanalı sendromu: Hodgkin lenfoma'da sarılığın nadir görülen bir nedeni

Yok olan safra kanalı sendromu, intrahepatik safra kanallarında progresif harabiyet ve kaybolma sonucunda gelişen, uzamış kolestazla karakterize bozukluklar grubudur. Yok olan safra kanalı sendromu ile başvuran bir Hodgkin lenfoma'lı olguyu sunuyoruz. Hodgkin lenfomada karaciğer hasarı nispeten sık görülür. Ancak bu hastaların sadece küçük bir yüzdesinde sarılık gelişir. Bu durum, ilaç toksisitesi, hemoliz, malin hücrelerle direk invazyon veya yaygın tıkayıcı lenfadenopatilere bağlı gerçekleşir. Hodgkin lenfomada yok olan safra kanalı sendromu kolestazın nadir bir nedenidir. Hodgkin lenfomada yok olan safra kanalı sendromunun mekanizması iyi bilinmese de, en yüksek olasılıkla bir paraneoplastik etkiyle olmaktadır

Anahtar kelimeler: Yok olan safra kanalı sendromu, Hodgkin lenfoması, kolestaz

INTRODUCTION

Vanishing bile duct syndrome (VBDS) refers to a group of disorders which are characterized by prolonged cholestasis as a consequence of progressive destruction and disappearance of intrahepatic bile ducts. We present a case of Hodgkin's lymphoma (HL) presenting with VBDS. Liver damage is relatively common in HL. But only a small percentage of these patients develop jaundice. This may be secondary to drug toxicity, hemolysis, direct invasion by malignant cells or by extensive, obstructive lymphadenopathy. VBDS secondary to HL is a rare cause of cholestasis in these patients. The mechanism of VDBS in HL is poorly explained, but a paraneoplastic effect seems most likely.

CASE REPORT

A 40-year-old male patient with an unremarkable past medical history presented with 6 weeks of fatigue and lethargy. He reported a weight loss of

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about twenty pounds, night sweats, and low-grade fevers. He also complained of decreased appetite, but denied abdominal pain, nausea, vomiting or diarrhea. He had also noticed yellow discoloration of his eyes and skin. On systemic review, he denied any other significant complains.

Physical examination at admission revealed an ill-appearing male with a temp of 100.5 °F, pulse of 68, blood pressure of 127/82, and an oxygen saturation of 100% on room air. He was icteric and cervical lymph nodes were matted, fixed and enlarged (maximum size: 3.5 x 3 cm). Chest was clear to auscultation. S1 and S2 were audible with no murmur or gallops. Abdomen was soft, non-tender, with no hepatosplenomegaly.

His complete blood count and electrolytes were within normal limits. Liver function tests (LFTs) were elevated: alanine aminotransferase (ALT): 351 U/L (normal: 10-47), aspartate aminotransferase (AST): 132 U/L (normal: 10-47), alkaline phosphatase: 698 U/L (normal: 39-117), total bilirubin: 4.2 mg/dL (normal: 0-1.0), direct bilirubin: 2.5 mg/dL (normal: 0-0.4). Haptoglobin and lactate dehydrogenase (LDH) were within defined limits. Excisional biopsy of the cervical lymph node was positive for Hodgkin's lymphoma (HL). A positron emission tomography (PET) scan was done, which showed increased fludeoxyglucose (FDG) uptake in the spleen and lymph nodes on the both sides of the diaphragm. Bone marrow biopsy showed no abnormalities. Thus, a diagnosis of stage III lymphoma was made. However, the etiology of the elevated LFTs remained unclear. Serological tests for hepatitis A, B, C, E, antimitochondrial antibody (AMA), and anti-smooth muscle antibody (ASMA) were all negative. PET CT done for tumor staging showed no liver involvement. Ultimately, a liver biopsy was done that revealed intrahepatic cholestasis associated with ductopenia, consistent with a diagnosis of vanishing bile duct syndrome (VBDS). The patient was started on ABVD (adriamycin, bleomycin, vinblastine and dacarbazine), which resulted in normalization of his liver function tests (LFTs) gradually over the course of the next few months.

DISCUSSION

HL usually presents with weight loss, fatigue, night sweats, and lymphadenopathy; however, on rare occasions, jaundice may be the initial symptom. Cholestasis secondary to ductopenia is an uncommon, yet well-documented complication of HL. VBDS, also known as bile duct paucity syndrome, was first described in adults in 1988 by Ludwig et al (1). It is a group of acquired disorders characterized by progressive destruction of bile ducts resulting in ductopenia leading to cholestasis. By definition, VBDS requires loss of interlobular ducts in more than 50 percent of small portal tracts. In

Table 1. Classification of causes of vanishing bile duct syndrome

Congenital	**Drug Induced**
• Byler's disease	• Ampicillin
• Cystic fibrosis	• Augmentin
• Extrahepatic bile duct atresia	• Azathioprine
• von Meyenburg complex	• Carbamazepine
• Zellweger syndrome	• Clindamycin
	• Diazepam
Infectious	• Meropenem
• Cryptosporidium parvum	• Nevirapine
• Cytomegalovirus	• Ibuprofen
• Epstein-Barr virus	• Phenytoin
• Hepatitis B virus	• Sulpiride
• Rubella virus	• Tetracycline
• Sepsis	• Zonisamide
Neoplastic	**Immunologic**
• Hodgkin's lymphoma	• Graft versus host disease (GVHD)
• Histiocytosis X	• Liver allograft rejection
	• Primary biliary cirrhosis
	• Primary sclerosing cholangitis

addition to HL, other etiologies (2) such as genetic disorders, medications, infectious diseases, neoplasia, and autoimmune disorders can lead to VBDS. The causes of VBDS are listed in Table 1.

The underlying mechanism by which biliary epithelial cells are damaged and intrahepatic bile ducts are lost in HL has been a topic of much debate. There are two theories (3) that have been suggested to explain the pathophysiological mechanism of VBDS in HL. The first of which states that microscopic lymphoma cell infiltration of bile ducts and hepatic sinusoids results in direct bile duct damage (4). The second and the more popular theory suggests that release of toxic cytokines from lymphoma cells results in paraneoplastic bile duct damage. These cytokines (5) could cause bile duct damage directly or may result in the recruitment of other effector cells, which could in turn lead to bile duct destruction. The fact that portal tracts have few or no lymphoma cells in those with VBDS supports the second theory (6).

Since VBDS may result from a variety of underlying etiologies, the clinical presentation of this condition can be highly variable. Symptoms can range from general constitutional complains to more specific manifestations of cholestasis such as xanthelasmas and gallstone formation.

Although the diagnosis of VBDS can be suggested by imaging studies such as endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography (MRCP), liver biopsy is required to confirm the diagnosis. Diagnostic yield can be increased by immunostaining the pathological specimen with cytokeratin 7 and 19, both of which are capable of identifying biliary elements (7).

Treatment of VBDS depends on the underlying etiology and includes withdrawal of offending medications, immunosuppression (8), chemotherapy (9), or ursodeoxycholic acid (10, 11). In the presence of severe complications related to hepatic dysfunction, liver transplantation (12) may be needed.

VBDS secondary to HL is potentially reversible, with about 30% (13) of the patients demonstrating good lymphoma and liver outcomes after being referred for definitive therapy for HL. Eradication of HL seems to be the most important significant factor associated with improved chance of normalization of liver function and survival, therefore patients should proceed early on, with the definitive treatment of HL. Our patient responded well to treatment for his HL and his liver function gradually normalized.

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