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Vanishing Bile Duct Syndrome in Hodgkin's Lymphoma: A Single Center Experience and Clinical Pearls

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To the Editor

Vanishing bile duct syndrome (VBDS) is a rare disease with a poorly understood pathophysiology. It is an acquired condition defined by the loss of intra-hepatic bile ducts leading to ductopenia and cholestasis.[1] The syndrome has been described in a variety of pathologic conditions including infection, ischemia, autoimmune disease, drug reaction, allograft rejection, and malignancy.[2] Prognosis is variable and dependent on the etiologic trigger of biliary epithelial apoptosis and capacity for biliary regeneration. Despite this, VBDS is often progressive resulting in biliary cirrhosis, liver failure, and potentially death. During the course of a year, we encountered two patients at our tertiary care hospital with this rare syndrome. Both patients were ultimately found to have malignancy-associated VBDS.

The first individual was a 41-year-old woman with a history of recently diagnosed stage IIa nodular sclerosing Hodgkin's lymphoma (HL) who presented with progressive, intermittent epigastric pain, weight loss, and jaundice. Laboratory data revealed an initially mixed then later cholestatic pattern of liver injury. Further work up including serology, computed tomography (CT), and magnetic resonance cholangiopancreatography (MRCP) were unrevealing. Ultimately, liver biopsy revealed intact hepatic architecture without fibrosis but loss of the interlobular bile ducts without inflammation or a ductular reaction consistent with the diagnosis of VBDS. She underwent systemic chemotherapy with DHAP (dexamethasone, cytarabine, and cisplatin) with 50% dose reduced cytarabine and involved-field radiation therapy (IFRT) with 3000 cGy achieving remission of her HL. She was treated with ursodeoxycholic acid and cholestyramine without improvement in her cholestasis. She was then treated with rifampin, a pregnane C receptor (PXR) agonist, which

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led to a transient decrease in her bilirubin. Unfortunately, her cholestasis did not resolve, and she ultimately chose to return to her home country where we were later informed of her death.

The second individual was a 25 year-old man who presented with abdominal pain, bloody diarrhea, and jaundice. Similar to the first patient, serologic and imaging studies were unrevealing. Endoscopy revealed pan-colitis and liver biopsy was notable for cholestasis and loss of bile ducts consistent with the diagnosis of VBDS. When his cholestasis and pruritis failed to respond to medical management for a period of 3 months, liver transplantation evaluation was initiated. During the evaluation he was noted to have lymphadenopathy and was ultimately diagnosed with stage IIB HL by biopsy. He was treated at an outside institution with nitrogen mustard and high dose corticosteroids combined with radiation therapy. He achieved remission of his HL with intact liver function but persistent cholestasis. Completion of a liver transplantation evaluation and close follow-up were recommended. Of note, whole exome sequencing was performed and identified a heterozygous missense variant of undetermined significance in the macrophage stimulating 1 (MST1) gene. Primary sclerosing cholangitis has shown consistent association with common single-nucleotide polymorphism (SNPs) in the MST1 locus in population studies. Further research is needed to explore potential genetic predisposition and the risk for VBDS in this patient population.

These cases highlight two distinct presentations of HL-associated VBDS. Based upon our limited experience with VBDS, it is crucial for physicians to create a broad differential for patients with suspected VBDS including malignancy. VBDS may be a paraneoplastic phenomenon associated with HL that may present prior to the diagnosis of lymphadenopathy. Liver biopsy is critical for the diagnosis of VBDS and should not be deferred. Once the diagnosis is confirmed on biopsy, aggressive therapy in the setting of HL-associated VBDS is indicated as achieving remission is crucial. Adjunctive medical management of cholestasis and supportive care is also required. If hepatic injury/cholestasis does not recover and liver dysfunction is evident, liver transplantation should be considered. At this time, further research is needed to explore potential genetic predisposition/risk for VBDS. Ultimately, early recognition of potential underlying VBDS-associated malignancy, appropriate laboratory screening, early aggressive treatment, cholestasis management, and liver transplantation evaluation are paramount to achieve successful outcomes in patients with HL-related VBDS.

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