Deeper Insights Into Vanishing Bile Duct Syndrome in Lymphoma: A Perplexing Entity

Vishwanath Sathyanarayanan,[1] Wai Chin Foo,[2] Michelle Fanale,[1] Jason Westin[1]

Clinical Practice Points

- Vanishing bile duct syndrome is an unusual entity characterized by progressive destruction of the intrahepatic bile ducts (ductopenia), which ultimately results in cholestasis. The pathogenesis is unclear and related to immunologic injury of bile ducts. The prognosis is poor, and the case reports of many patients who died of the illness have been reported.
- We present a case to illustrate an important message that timely treatment with appropriate chemotherapy, despite the presence of liver dysfunction, can be lifesaving for critically ill patients with lymphoma associated with vanishing bile duct syndrome.
- Along with the case presentation, we provide an extensive review of published studies and the published data of cases to give a better understanding of this entity. Using the data from several of these anecdotal case reports, we formulated clinical guidelines to assist oncologists globally to treat this potentially curable disorder.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 16, No. 5, e65-70 © 2016 Elsevier Inc. All rights reserved.
Keywords: Chemotherapy, Hepatic dysfunction, Hodgkin lymphoma, Liver failure, Review

Case Report

A 39-year-old man presented to the emergency department in July 2013 with a 6-month history of intermittent fever, fatigue, weight loss of 30 lb, and drenching night sweats. He had been evaluated at various hospitals for fever of unknown origin. He also reported a new onset of jaundice that had developing during the 2 weeks before admission. He denied any potentially hepatotoxic medications, recent or chronic alcohol intake, illicit intravenous drug use, or any family history of liver disease. He was hypotensive and tachycardic on arrival. Contrast-enhanced computed tomography (CT) scanning of the chest, abdomen, and pelvis revealed nonbulky adenopathy above and below the diaphragm, including a para-aortic lymph node measuring 4.5 × 4.2 cm, hepatosplenomegaly without a focal liver mass or evidence of dilated hepatic ducts, and a small indeterminate lesion in the spleen.

Because of his hypotension and severe jaundice, he was admitted to the intensive care unit for resuscitation and urgent workup. His initial laboratory values were noted for a total bilirubin of 10 mg/dL, alkaline phosphatase of 497 U/L (upper limit of normal, 126 U/L), aspartate aminotransferase of 85 U/L (upper limit of normal, 46 U/L), and alanine aminotransferase of 63 U/L (upper limit of normal, 56 U/L). He was also coagulopathic, with a prothrombin time of 15.4 seconds (range, 12.7-15 seconds) and an activated partial thromboplastin time of 46.2 seconds (range, 24.7-35.9 seconds). A viral hepatitis panel was nonreactive for hepatitis C antibody and hepatitis B surface antigen, and he was confirmed to be human immunodeficiency virus negative. Cytomegalovirus antigen was negative by polymerase chain reaction. Other infectious disease panels, including rickettsia, Q fever, coccidioidomycosis, blastomycosis, and cryptococcosis, were negative. Antinuclear antibody and rheumatoid factor were negative. A CT-guided biopsy of the retroperitoneal lymph node showed classic Hodgkin lymphoma (HL) and nodular sclerosis. He was diagnosed with stage IIIB HL with an international prognostic score of 4.

During his initial evaluation, fluid resuscitation administration, and while awaiting the pathology results, his bilirubin continued to increase. The peak total bilirubin reached 21.8 mg/dL (direct, 20.5 mg/dL), alkaline phosphatase of 559 U/L, and transaminases of aspartate aminotransferase of 103 U/L and alanine aminotransferase of 116 U/L. In addition, he developed acute kidney injury without a clear etiology, for which the nephrology service was consulted. Emergency hemodialysis was administered for rapidly worsening metabolic acidosis. During his admission in the intensive care unit, he developed severe hypotension without a clear infectious etiology

[1]Division of Cancer Medicine, Department of Lymphoma/Myeloma
[2]Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, TX

Submitted: Dec 16, 2015; Accepted: Feb 18, 2016; Epub: Feb 27, 2016

Address for correspondence: Jason Westin, MD, MS, Division of Cancer Medicine, Department of Lymphoma/Myeloma, MD Anderson Cancer Center, 1400 Holcombe Boulevard, Unit 0429, Houston, TX 77030
E-mail contact: jwestin@mdanderson.org

2152-2650/$ - see frontmatter © 2016 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.clml.2016.02.035

that required vasopressor therapy to maintain an acceptable blood pressure. The patient also developed moderate respiratory insufficiency, which was managed with oxygen using nasal cannula, and he did not require intubation. A transjugular liver biopsy was obtained to evaluate the etiology of his severe liver dysfunction. The biopsy examination showed cholestasis and portal inflammation with injured, but intact, bile ducts (Figure 1). No histologic or immunohistochemical support was provided for the direct involvement of the liver by the HL.

Because his condition continued to rapidly decline despite maximal supportive care, the patient was offered to initiate chemotherapy for HL, even with his multisystem organ failure. Because of his severe hepatic dysfunction, his therapy was initiated with mechlorethamine 6 mg/m^2 intravenously for 2 doses, which resulted in rapid improvement in his liver function (Figure 2). His bilirubin had decreased to 13.4 mg/dL by day 9 and was 3.5 mg/dL by day 14. In addition, his renal function had improved, and he no longer required hemodialysis after day 19. Once his total bilirubin had decreased to < 3 mg/dL, he was treated with Adriamycin, vinblastine, and dacarbazine (AVD). Bleomycin was omitted because of his resolving respiratory insufficiency. For cycle 1A, he received a 50% dose reduction of the chemotherapy drugs because of his resolving hepatic insufficiency and renal failure. Cycle 1A was tolerated well without any acute or delayed therapy-related toxicities. He was able to be discharged from the hospital and received cycle 1B of AVD, with a 25% dose reduction, as an outpatient. His liver and renal function completely normalized, and he subsequently received an additional 5 cycles of AVD at 100% of the routine dosage without any significant therapy-related toxicity. After 2 cycles of AVD, an interim fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET)/CT scan showed no residual FDG-avid disease. After completion of 6 cycles of AVD, an FDG-PET/CT scan confirmed that he had achieved a complete metabolic response with no residual disease visible. At the last follow-up visit, the patient was 26 months after therapy and was doing well with no evidence of HL relapse. His liver function test results remained within normal limits.

Discussion

Lymphomas, including both HL and non-HL (NHL), can cause hepatic dysfunction, ranging from asymptomatic elevation of liver enzymes to fulminant liver failure.[1,2] Hepatic involvement can be seen in 20% of liver biopsy specimens and 50% of necropsies in patients with NHL. The frequency of hepatic involvement in HL can vary. Liver infiltration in Hodgkin disease has been observed in 5% to 8% of cases, and in autopsy series, the range has been as high as 30% to 70%. Cholestasis as the presenting symptom of HL is uncommon (< 4%).[3-6]

Lymphoma-associated liver dysfunction is multifactorial and has a wide spectrum of manifestations, ranging from asymptomatic abnormal liver function test results to acute liver failure. The etiology of this dysfunction can be related to infiltration of the liver by lymphoma, extrinsic compression by lymphadenopathy at the porta hepatis, or as a consequence of an immune-mediated or paraneoplastic process characterized by ductopenia, known as the vanishing bile duct syndrome (VBDS). In addition, indirect entities can develop that can mimic hepatic dysfunction, such as autoimmune hemolysis resulting in jaundice.

The purpose of the present report was to study VBDS with an illustrative case to improve the understanding of this entity and also to formulate guidelines for the treatment of lymphoma associated with VBDS using the findings from anecdotal case reports published to date.

VBDS is an uncommon entity characterized by progressive destruction of the intrahepatic bile ducts (ductopenia), which ultimately results in cholestasis.[7] The case series reported by Hubscher et al[8] in 1993 was a landmark study that paved the way for understanding the mechanisms of this intriguing entity. Most reported cases of VBDS have occurred in patients with HL, with very few cases reported to occur in patients with NHL.[8] The etiologic relationship between HL and VBDS remains unclear. The most widely cited hypothesis is that a cell-mediated immunologic process through lymphoma-derived cytokines can cause ductopenia as a paraneoplastic manifestation. This hypothesis has been supported by the finding that few liver biopsies of VBDS have demonstrated

Figure 1 Microscopic Examination of the Liver Biopsy Showing (A) an Intact but Injured Bile Duct (Arrow) in a Background of a Mixed Inflammatory Infiltrate and (B) Cholestasis