Vanishing Bile Duct Syndrome Presenting as a Paraneoplastic Phenomenon in Classical Hodgkin's Lymphoma: Importance of Early Recognition in Improving Outcome and Preventing Liver Failure

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Abstract:
Herein we present a unique case of Vanishing Bile Duct Syndrome (VBDS) in the setting of Classical Hodgkin Lymphoma, in a 32 year old woman, who initially presented to the emergency department for chief complaint of jaundice and migraine. The diagnosis of VBDS was made by liver biopsy, review of literature, and using the diagnostic criteria for VBDS.

Introduction:
According to LiverTox, Vanishing Bile Duct Syndrome (VBDS) is a serious clinical complication, most commonly associated with drug induced liver injury (DILI), characterized by chronic cholestasis and histologic loss of intrahepatic bile ducts that can be accompanied with immunoallergic features.[1] The presentation of VBDS occurs as a result of direct liver insult, presenting between 1-6 months following DILI. Typically, patients present with jaundice, fatigue, pruritus, hypercholesterolemia and skin xanthomata. Laboratory findings may include persistently elevated alkaline phosphatase levels and bilirubin despite an improvement in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels. Although a majority of cases documented in literature are related to DILI, alternative causes have been recorded. There are few documented cases of VBDS associated with Hodgkin's lymphoma. A case of a 25-year-old man found to have classical stage IIB Hodgkin's Lymphoma with VBDS on liver biopsy.[2] This patient underwent nitrogen mustard and high dose corticosteroids combined with radiation and gemcitabine and oxaliplatin. He achieved remission of Hodgkin's Lymphoma, however had persistent cholestasis and portal hypertension seen on liver biopsy.

The clinical course of VBDS can vary from transient elevations of liver chemistries to progressive disease of severe cholestasis and liver failure requiring transplant. While recovering clinically, patients may still show persistent elevation of alkaline phosphatase and bilirubin until the underlying cause is addressed. Irreversible bile duct loss can potentially lead to biliary cirrhosis and hepatic failure. If biliary epithelial regeneration occurs, recovery could take months to years.[2]

The three classic, diagnostic criteria for VBDS include 1) Persistent elevations in serum alkaline phosphatase and bilirubin for more than 6 months after onset of drug induced liver disease. 2) The absence of clinical or serologic evidence of primary biliary cholangitis, sclerosing cholangitis and graft-vs-host disease. 3) Liver biopsy findings of paucity of intralobular bile ducts (<50% of portal areas with bile duct in a biopsy with at least 10 portal areas) in a sample taken at least 1 month after onset of injury. Milder forms may show a decrease in bile ducts with 50-70% of portal areas having an identifiable intralobular bile duct.[1]

There are several drug classes that may contribute to the development of VBDS, including certain antibiotics, anticonvulsants, hormone replacement therapy, antidepressants, non-steroidal anti-inflammatory drugs, enalapril, hydrochlorothiazide, and several more.[1,3] Differential diagnosis should include drug induced VBDS, severe graft-vs-host disease, Hodgkin Lymphoma, primary sclerosing cholangitis, and primary biliary cholangitis.[4] The three main causes of intrahepatic cholestasis in association with lymphomas are hepatic lymphoma, VBDS, and paraneoplastic phenomenon. Secondary hepatic lymphoma is an end stage process which can rapidly lead to fulminant hepatic failure whereas primary hepatic lymphoma has a worse prognosis and outcome, and occurs in the absence of extrahepatic disease.[5] VBDS in the setting

of Classical Hodgkin Lymphoma is seen as a paraneoplastic process with great potential for liver failure and death.[6] Prompt identification and treatment initiation is critical to therapy in this patient subset. Hodgkin's Lymphoma is a lymphoid neoplasm derived from B cells. The cellular microenvironment is key to the accurate diagnosis and to the pathophysiology of this disease process. All subtypes of Hodgkin's Lymphoma share a common phenotype. Commonly used diagnostic markers are CD30 and CD15.[7,8]

Case Presentation:

This patient is a 32 year old woman who presented to our facility from the emergency department of an outlying hospital with a chief complaint of yellowing of the eyes and skin, and migraine with a past medical history of severe recurrent major depressive disorder, anxiety, and post traumatic stress disorder. At the time of presentation, she reported that her migraine had begun the previous week and led her to present to the emergency department then for a migraine. She was prescribed compazine and sumatriptan at that time with minimal improvement in her symptoms. On initial history of present illness review, the patient reported alternating ibuprofen, Excedrin, and Tylenol with minimal relief. In the preceding three days, she had developed clay colored stools and yellowing of her eyes and skin. At the outlying facility, she was found to have elevation of liver chemistries in a cholestatic pattern; AST: 146, ALT: 159, Alkaline Phosphatase: 886, total bilirubin: 12.6, direct bilirubin 7.5, total protein: 8.52. Initial Computed Tomography (CT) scan of abdomen and pelvis without contrast at the outlying facility showed moderate stool and gastric distention with enteric contents, without acute findings. Specifically, the spleen, pancreas, liver, adrenals, and kidneys demonstrated no acute abnormality on unenhanced examination. CT head without contrast was negative for acute pathology. Right upper quadrant ultrasound demonstrated cholelithiasis without sonographic evidence of acute cholecystitis. Magnetic resonance cholangiopancreatography (MRCP) showed a 1 cm filling defect of the gallbladder body, favoring cholelithiasis without common biliary ductal dilation, intrahepatic ductal dilation, or choledocholithiasis.

The following labs were unremarkable: acute viral hepatitis panel, serum ceruloplasmin (50), carcinoembryonic antigen (CEA), carbohydrate antigen (CA 19-9), Filamentous-actin (F-actin), Immunoglobulin G (IgG), anti-mitochondrial antibody, leptospira and toxocara antibodies, acetaminophen level, salicylate level, and ammonia. Other labs of note included urine drug screen that was positive for benzodiazepines and cannabinoids, serum copper level: 241.8 (upper limit of normal 150), hemoglobin 11.3, transferrin: 190, iron: 47, total iron binding capacity (TIBC): 283, iron saturation: 16.6. The patient then left against medical advice after a two day hospitalization and presented to a different facility approximately 45 days later. She followed with a Gastroenterology outpatient clinic after leaving her first hospital admission with continued elevation of liver chemistries and findings on MRCP. Between hospitalizations, the patient began taking over the counter supplements for her liver abnormalities ("stone free"), which include ingredients such as turmeric root, dandelion whole plant extract, coin leaf desmodium aeriel parts, ginger root, lemon balm leaf, marshmallow root extract, parsley root and licorice root extract. She once again presented with leukocytosis (WBC: 14.9) and anemia with hemoglobin 10.7 and mild thrombocytosis platelets 465**.** Alpha-1-antitrypsin: 318 (upper limit of normal 300), anti-neutrophil cytoplasmic antibody negative, immunoglobulin study negative and antinuclear antibody negative. She reported feeling worse with generalized weakness, abdominal discomfort, and itching sensation.

In continuation of diagnostic evaluation, a liver biopsy showed moderate centrilobular cholestasis without ongoing injury, and evidence of mild to moderate reticulin collapse with near-complete regeneration and healing. 14 of 21 portal tracts with intact bile ducts (67%) were noted on liver biopsy pathology. All visible bile ducts were very atrophic, but intact and without inflammatory injury or viral cytopathic effect. Biopsy was negative for inflammation, steatosis, or significant fibrosis (modified Brunt's stage 0/4). Biopsy was consistent with DILI and no lymphomatous involvement seen in liver biopsy. On a second pathologist review, the diagnosis of VBDS was made.

Liver function tests followed a cholestatic pattern without evidence of obstruction, and the patient was empirically started on ursodeoxycholic acid. Hematology service was consulted for leukocytosis with a stress-induced trend, elevated international normalized ratio (INR), and elevated partial thromboplastin time (PTT). Mixing study was performed for the PTT and was noted to be positive for possible underlying inhibitors. To further complicate the patient's clinical course, there was also concern for potential acquired inhibitors of prothrombin, fibrinogen, factor V or factor X, with the concern of amyloidosis associated factor X deficiency. Chest x-ray showed pulmonary infiltrates and follow up CT showed evidence of anterior, middle, and posterior mediastinal adenopathy with the largest node being a right paratracheal node measuring 2.8cm, potentially representative of underlying lymphoproliferative malignancy, which could include formation of factor inhibitors.

The patient was started on steroids for potentially acquired inhibitor formation against factor Xa and prothrombin. Biopsy of lymph nodes showed Classical Hodgkin's Lymphoma, nodular sclerosis subtype with large atypical lymphoid cells positive for CD30 with CD15 appearing to be positive within a subset of neoplastic cells. CT showed supraclavicular and mediastinal adenopathy with suspected lymphomatous involvement with low-density lesions in the spleen. The patient was diagnosed with Classical Hodgkin Lymphoma stage IIIB. Further staging with bone marrow biopsy showed hypercellular marrow with trilineage hematopoiesis but was negative for lymphoma. VBDS was treated with ursodeoxycholic acid and steroids. Although initiated for a different diagnosis, it certainly helped to improve cholestasis.

Due to the patient's significant hepatic dysfunction and elevated bilirubin, the patient was initially deemed not a candidate for adriamycin, bleomycin, vinblastine, dacarbazine (ABVD) and an alternative regimen with cisplatin followed by cytarabine and dexamethasone was initiated. Repeat MRCP showed no abnormality in the liver and pathology did not reveal hepatic involvement of lymphoma. On review of pathology, the patient met criteria for VBDS as previously discussed above. Diagnosis was supported by lymphoma and VBDS, with no other obvious attributable cause to the patient's hepatic dysfunction. The patient developed tumor lysis syndrome and was treated prior to discharge from the hospital and continues to follow up out-patient with Oncology and is continuing chemotherapy. Total bilirubin is showing a downward trend and the patient appears to be responding to current treatment that was adjusted to ABVD therapy. Patient's restaging scan shows an excellent response to combination therapy at this time with significant reduction in size of lymphadenopathy noted in hilar and mediastinal areas.

Discussion:
This case report demonstrates a case of vanishing bile duct syndrome in the setting of Hodgkin's Lymphoma. The patient's initial presentation was concerning for DILI, however as the hospitalization course progressed, it became clear through lymph node biopsy that this patient had Classical Hodgkin's Lymphoma. Liver biopsy showed moderate centrilobular cholestasis without ongoing injury and showed 14 of 21 portal tracts with intact bile ducts. All visible bile ducts were atrophic and biopsy was negative for fibrosis, steatosis, inflammation, and no lymphoma in the liver. This patient had persistent elevations in alkaline phosphatase and bilirubin greater than six months, did not show evidence of alternative liver pathology, and was indicative of milder VBDS with 67% of portal tracts with intact bile ducts noted on liver biopsy pathology. Intrahepatic cholestasis and vanishing bile duct syndrome are two separate diagnoses, however, intrahepatic cholestasis can progress to VBDS.[9] Prompt recognition of VBDS as a paraneoplastic syndrome of Classical Hodgkin's Lymphoma early in the clinical presentation is very important for better outcome, as it influences the choice of chemotherapy for Hodgkin's and also in prevention of liver failure. The patient is showing excellent response to treatment at this time and is being followed with restaging scanning. A previous case reported did show a return to normal hepatic function after completion of ABVD therapy when assessing liver function testing up to six years later.[4] There are several reports of patients in whom following completion of chemotherapy, liver function returned to baseline or normal in most cases of Hodgkin's Lymphoma and Vanishing Bile Duct Syndrome.

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All identifying information has been removed from this case report to protect patient privacy.

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