Vanishing bile duct syndrome in Hodgkin’s lymphoma: A case report and literature review

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Abstract
Vanishing bile duct syndrome (VBDS) has been described in different pathologic conditions including infection, ischemia, adverse drug reactions, autoimmune diseases, allograft rejection, and humoral factors associated with malignancy. It is an acquired condition characterized by progressive destruction and loss of the intra-hepatic bile ducts leading to cholestasis. Prognosis is variable and partially dependent upon the etiology of bile duct injury. Irreversible bile duct loss leads to significant ductopenia, biliary cirrhosis, liver failure, and death. If biliary epithelial regeneration occurs, clinical recovery may occur over a period of months to years. VBDS has been described in a number of cases of patients with Hodgkin’s lymphoma (HL) where it is thought to be a paraneoplastic phenomenon. This case describes a 25-year-old man found on liver biopsy to have VBDS. Given poor response to medical treatment, the patient underwent transplant evaluation at that time and was found to have classical stage II B HL. Early recognition of this underlying cause or association of VBDS, including laboratory screening, and physical exam for lymphadenopathy are paramount to identifying potential underlying VBDS-associated malignancy. Here we
review the literature of HL-associated VBDS and report a case of diagnosed HL with biopsy proven VBDS.

Key words: Cholestasis; Bile ductopenia; Vanishing bile duct syndrome; Hodgkin’s lymphoma; Liver

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Core tip: Vanishing bile duct syndrome (VBDS) is a rare form of liver injury and can be caused by multiple etiologies including malignancy. It is therefore critical for physicians to create a broad differential when VBDS is suspected and diagnosed. Liver biopsy is critical and should not be deferred. Once the diagnosis of VBDS is confirmed on biopsy, aggressive therapy, adjunctive medical management of cholestasis, and supportive care is indicated as achieving remission and symptom management in Hodgkin’s lymphoma-associated VBDS is crucial. If hepatic recovery does not occur, liver transplantation should be considered.

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INTRODUCTION

Vanishing bile duct syndrome (VBDS) refers to a group of acquired disorders associated with progressive destruction and disappearance of the intrahepatic bile ducts leading to cholestasis[1]. Although the pathogenesis is poorly understood, VBDS has been associated with potential infectious etiologies, ischemia, autoimmune diseases, adverse drug reactions, and humoral factors associated with malignancy (Table 1)[2]. Hodgkin’s Lymphoma (HL)-related VBDS is thought to be a paraneoplastic process which typically presents with jaundice, pruritus, and weight loss[3]. Here we extensively review available literature addressing HL-associated VBDS and report a case of HL with biopsy proven VBDS.

CASE REPORT

A 25-year-old man with past medical history significant for depression presented to the hospital with two-weeks of nausea and abdominal discomfort accompanied by loose, blood-tinged stools, and tenesmus. He denied recent travel and family history was only significant for a distant cousin with ulcerative colitis. The patient worked as a baker in a local pastry shop. He reported active tobacco use, social alcohol consumption, and occasional marijuana use, though no illicit substance abuse. His medications included bupropion for depression and omeprazole for occasional reflux symptoms.

On initial physical exam, he was noted to be febrile to 102 degrees Fahrenheit, markedly jaundiced with icteric sclera bilaterally, and tenderness to palpation in the epigastric region of his abdomen without rebound, guarding, or organomegaly. The remainder of his exam was unremarkable aside from mild bipedal edema. Labs were significant for alkaline phosphatase (ALP) of 818 U/L, total protein of 2.5 g/dL, alanine aminotransferase (ALT)/aspartate aminotransferase (AST) of 146/144 U/L, total bilirubin/direct bilirubin of 6.2/3.9 mg/dL, and INR of 2.23. Remaining laboratory data including the complete blood count were within normal limits. Stool studies were negative other than positive fecal leukocytes. Viral hepatitis panel, anti-nuclear antibody (ANA), and an aceterminophen level were also negative.

Computerized tomography (CT) of the abdomen and pelvis showed mild to moderate circumferential thickening of the entire colon without peri-colonic fat stranding. Given the cholestatic pattern, magnetic resonance cholangiopancreatography (MRCP) was obtained and unremarkable. The patient underwent a colonoscopy that showed no focal ulcers, but continuous erythema and edema of the mucosa from rectum to the cecum consistent with a pan-colitis. The terminal ileum was also noted to be inflamed. Random biopsies suggested epithelial injury secondary to ischemia, drug/toxin effect, or an enteroinvasive infection.

During the patient’s hospital course, his coagulopathy was corrected with phytanadione, his liver function remained stable, and abdominal pain resolved with supportive care. He was subsequently discharged; however, the patient was re-admitted with worsening cholestasis in setting of Influenza A. He was treated with oseltamivir and was initiated on ursodeoxycholic acid. ALP remained elevated at 501 U/L, while liver enzymes down trended (ALT/AST of 77/55 U/L). Despite this, the patient was found to have a worsening hyperbilirubinemia (total bilirubin/direct bilirubin of 6.2/3.9 mg/dL). Liver biopsy was obtained, which showed cholestatic hepatitis with ductopenia, consistent with VBDS (Figure 1).

Given a static course without improvement over a three month period and follow-up biopsy noting persistent ductopenia, liver transplant workup was initiated. CT chest performed during transplant evaluation revealed a soft tissue density mass in the left hilar region. Biopsies of the lymph node confirmed classical stage II B HL. He later developed worsening edema which was attributed to nephrotic syndrome. He began treatment at an outside facility with nitrogen mustard and high dose corticosteroids combined with radiation therapy and ultimately gemcitabine/oxaliplatin for disease outside of chest. The patient responded to treatment and achieved remission of HL. However, he
has had persistent cholestasis and a recent transjugular liver biopsy revealed portal hypertension, continued bile duct loss and an increase in ductular proliferation and sinusoidal fibrosis. He has ascites and a Model for End Stage Liver Disease - Sodium score most recently of 23. The goal of current therapy is to manage portal hypertension and hope to achieve a recurrence free interval to consider future transplantation.

The patient subsequently underwent extended genetic panel sequencing to evaluate potential molecular defects in bile acid transport or synthesis. Next-generation whole exome sequencing identified a heterozygous missense variant of undetermined significance in the macrophage stimulating (MST1) gene, C265Y (chromosome 3: 49724179, TGC>TAC, hg19). This change is located in a highly conserved residue in evolution and is not found in the general population. Primary sclerosing cholangitis (PSC) and inflammatory bowel disease (IBD) show consistent association with common single nucleotide polymorphisms in the MST1 locus in population studies. The significance of rare variants in this gene is not known in the context of PSC or IBD and is a unique finding that may have a future role in testing in similar clinical presentations.

**DISCUSSION**

Here we present a case of VBDS in the setting of HL. The association between VBDS and HL, first detailed in 1993 by Hubscher et al [4], has subsequently been described in a number of published cases to date (Table 2) [3-39]. The first three patients, described by Hubscher et al [4], ultimately progressed to hepatic failure [4]. Even when hepatic failure does not occur, VBDS associated with HL may predict poor overall survival and prognosis.

Hepatic involvement with HL may be seen in as many as 50% of patients. Though VBDS is rare, liver

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**Table 1 Causes of vanishing bile duct syndrome**

| Classification     | Causes                                                                                      |
|--------------------|---------------------------------------------------------------------------------------------|
| Medications        | Non-FDA approved weight loss supplements, sertraline, temozolomide, oxcarbazepine, levofloxacin, ibuprofen, sulfamethoxazole-trimethoprim, meropenem, lamotrigine, valproic acid, azithromycin, moxifloxacin, chlorpromazine, carbamazepine, interferon, mycophenolate mofetil, anabolic steroids, allopurinol |
| Infections         | Human immunodeficiency virus (HIV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), cryptosporidium, reovirus type 3 |
| Malignancy         | Lymphoma (B-cell, T-cell rich B-cell, Hodgkin’s, non-Hodgkin’s, and anaplastic large cell) |
| Immunologic        | Primary biliary cholangitis, primary sclerosing cholangitis, sarcoidosis, chronic graft vs host disease |

*Not a comprehensive list.*

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**Figure 1 Liver biopsy.** A: The lobular parenchyma has marked cholestasis (arrow) with a zone 3 accentuation, associated with occasional feathery hepatocyte degeneration (arrowhead) and mild inflammation; B: Portal tract with portal vein (arrow) and two branches of hepatic arterioles (arrowheads) with missing bile duct; C: Ito cell lipidosis (arrowheads) were also seen. Hematoxylin-eosin staining, magnification × 200.
injury in VBDS has a high mortality in an otherwise curable disease. Other conditions that may cause jaundice in HL include biliary obstruction secondary to lymph node enlargement, hemolysis, and other viral illnesses, most commonly cytomegalovirus. While hepatic failure is a major cause of mortality amongst patients with HL-related VBDS, many of the case reports reviewed noted complete remission with lymphoma treatment and improvement of hepatic function.

Patients with HL-related VBDS typically present with jaundice, pruritus, and weight loss as seen in the patient reported above. Treatment revolves around treating the underlying cause. Appropriate therapy

| Author                  | Year | Liver biopsy | HL treatment (chemotherapy and/or XRT) | Outcome/cause of death               |
|-------------------------|------|--------------|---------------------------------------|-------------------------------------|
| Our patient             | 2014 | VBDS         | Yes                                   | Remission                           |
| Rota Scalabrini D       | 2014 | VBDS         | Yes                                   | Remission                           |
| Nader K                 | 2013 | VBDS         | Yes                                   | Death/hepatic failure and sepsis    |
| Aleem A                 | 2013 | VBDS         | Yes                                   | Death/hepatic failure               |
| Wong KM                 | 2013 | VBDS         | Yes                                   | Remission                           |
| Umit H                  | 2009 | VBDS         | Unknown                               | Unknown                             |
| Pass AK                 | 2008 | VBDS         | Yes                                   | Remission/awaiting liver transplant |
| Leeuwenburgh I          | 2008 | VBDS         | Yes                                   | Death/aspiration                    |
| DeBenedet AT            | 2008 | VBDS         | Yes                                   | Death/unknown                       |
| Ballonoff A             | 2007 | VBDS         | Yes                                   | Remission                           |
| Berta SK                | 2006 | IC           | Yes                                   | Remission                           |
| Schmitt A               | 2006 | VBDS         | No                                    | Death/sepsis                        |
| Han WS                  | 2005 | VBDS         | Unknown                               | Recurrent HL                        |
| Cordoba Iturriagagaitia A | 2005 | VBDS     | Unknown                               | Remission                           |
| Guliter S               | 2004 | VBDS         | Yes                                   | Death/sepsis                        |
| Liangpunsakul S         | 2002 | Cholestatic hepatitis | Yes                             | Remission                           |
| Komurcu S               | 2002 | VBDS         | Yes                                   | Death/hepatic failure               |
| Ripoll C                | 2002 | VBDS         | Yes                                   | Death/hepatic failure               |
| Ripoll C                | 2002 | VBDS         | Yes                                   | Remission                           |
| Ozkam A                 | 2001 | VBDS         | Yes                                   | Death/hepatic failure               |
| Allory Y                | 2000 | VBDS         | Unknown                               | Death/sepsis                        |
| Rossini MS              | 2000 | VBDS         | Yes                                   | Death/hepatic failure               |
| Yusuf MA                | 2000 | VBDS         | Yes                                   | Death/hepatic failure               |
| Dourakis SP             | 1999 | Hepatocellular necrosis | Yes                             | Death/hepatic failure               |
| Yalcin S                | 1999 | IC           | No                                    | Death/sepsis                        |
| Yalcin S                | 1999 | IC           | Yes                                   | Remission                           |
| De Medeiros BC          | 1998 | VBDS         | Yes                                   | Death/hepatic failure               |
| De Medeiros BC          | 1998 | VBDS         | Yes                                   | Remission                           |
| Croshie OM              | 1997 | VBDS         | Yes                                   | Remission                           |
| Gottrand F              | 1997 | VBDS         | No                                    | Death/hepatic failure               |
| Warnier AS              | 1994 | IC           | Yes                                   | Remission                           |
| Jansen PLM              | 1994 | IC           | Yes                                   | Death/variceal hemorrhage           |
| Hubscher SG             | 1993 | VBDS         | Yes                                   | Death/pneumonia                     |
| Hubscher SG             | 1993 | VBDS         | Yes                                   | Death/unknown                       |
| Hubscher SG             | 1993 | VBDS         | Yes                                   | Death/sepsis                        |
| Birrer MJ               | 1987 | IC           | Yes                                   | Death/sepsis                        |
| Lieberman DA            | 1986 | IC           | No                                    | Death/respiratory arrest            |
| Trevby PN               | 1979 | IC           | Yes                                   | Remission                           |
| Trevby PN               | 1979 | Mild portal hepatitis | No                        | Death                                |
| Trevby PN               | 1979 | Lymphoma infiltration | Yes                      | Death                                |
| Trevby PN               | 1979 | Lymphoma infiltration | No                        | Death                                |
| Trevby PN               | 1979 | Mixed inflammatory and atypical histiocytes | Yes                     | Remission                           |
| Trevby PN               | 1979 | IC           | Yes                                   | Death/hepatic failure               |
| Piken EP                | 1979 | IC           | Yes                                   | Death/unknown                       |
| Perera DR               | 1974 | IC           | Yes                                   | Death/hepatic failure               |
| Perera DR               | 1974 | IC           | Yes                                   | Remission                           |
| Perera DR               | 1974 | IC           | Yes                                   | Remission                           |
| Groth C                 | 1972 | IC           | Yes                                   | Death/hepatic failure               |
| Juniper K               | 1963 | IC           | Yes                                   | Death/hepatic failure               |
| Bouroncle B             | 1962 | IC           | Yes                                   | Death/hepatic failure               |
| Bouroncle B             | 1962 | IC           | Yes                                   | Death/hepatic failure               |

HL: Hodgkin’s lymphoma; VBDS: Vanishing bile duct syndrome; IC: Idiopathic cholestasis.

Table 2 Reported literature involving the association between vanishing bile duct syndrome and Hodgkin’s lymphoma
must balance the need for aggressive chemoradiation to achieve remission but is also limited by the degree of liver dysfunction. Treatment and decisions on when to treat remain difficult as there exists a delicate balance between aggressive chemoradiation regimens and worsening cholestasis. Many previous cases published in the literature utilized full dose chemotherapy or a reduced dose to treat the underlying malignancy. Despite a difference in dosage, some patients were cured while others succumbed to liver failure.

Radiotherapy has been shown to improve liver failure free survival. While chemoradiation is a treatment option, many cases ultimately lead to significant liver dysfunction requiring liver transplantation. Some authors feel HL-associated VBDS is irreversible and patients should therefore be considered for liver transplantation regardless of remission, though this remains controversial given the limited data and rarity of this syndrome. Pass et al[29] reported on a patient awaiting liver transplant however the outcome of this case is unknown. They reported that early measures should be taken to prepare for liver transplant starting with aggressive treatment for HL remission with subsequent liver transplant evaluation. Our patient did not receive treatment at our institution though sought treatment with MOPP (mechlorethamine, vincristine, procarbazine, and prednisone). He showed improvement in regards to biliary regeneration and liver function and will be followed for consideration for liver transplantation should this become necessary.

The decision and timing of treatment of this disease is a challenge. The preferred treatment of HL-related VBDS is complex and controversial, driven largely by the fact that the mechanism of VBDS in HL remains unclear. Differing theories have proposed cell-mediated immunologic reactions or toxic cytokines derived from lymphoma cells that lead to ductopenia. Alternative proposals postulate biliary epithelial cells are damaged due to cross reactive T cells recognizing auto-antigens leading to apoptosis of biliary epithelium. Previous studies have shown the expression of major histo-compatibility complex as well as intercellular adhesion molecules in response to cytokines produced by HL. Given the presumed immunological reaction causing VBDS, treatments targeting this response have been attempted. Rituximab, a chimeric monoclonal antibody against CD20 frequently expressed in HL, has been used with positive outcomes. Rituximab may have a therapeutic role in CD20-negative patients given this presumed immunological reaction causing VBDS. Apheresis treatment, in addition to chemotherapy and radiotherapy, has also been reported effective in curing patients with VBDS.

VBDS, colitis, and later nephrotic syndrome diagnosed in the setting of volume overload and edema, were all believed to be paraneoplastic manifestations of our patient’s underlying HL. Based upon the literature review and our patient’s presentation, cholestasis appears to be the predominant symptom of HL in patients who were found to have VBDS. This has been previously described by Hallén et al[46] who reported on a patient with severe hyperbilirubinemia in the setting of VBDS with subsequent diagnosis of HL. Strategies to improve cholestasis such as ursodeoxycholic acid and cholestyramine may benefit patient’s symptoms though limited data exists. Other treatment options have been recommended including rifampin which can improve bilirubin levels and symptoms of pruritus. Hallén et al[46] additionally described the use of bilirubin apheresis treatment with an anion exchange adsorbent column for the reduction of bilirubin and bile acids with good symptomatic effect.

In summary, this case highlights the importance of exercising an exhaustive investigation into all potential causes of VBDS when the diagnosis is made - especially underlying malignancy[48]. Based on previous published case presentations, patients do not appear to recover from impaired liver function without achieving a complete remission of HL. This highlights the need for practitioners to be aware of the association of HL with VBDS and evaluate patients with such presentation for underlying malignancy. Early recognition of this association, appropriate laboratory screening, and survey for lymphadenopathy are critical to identifying HL-associated VBDS[8,29]. Early aggressive treatment and regeneration of the biliary epithelium are paramount to achieve a successful outcome.

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The authors have nothing to disclose. All authors listed have contributed sufficiently to the project to be included as authors, and all those who are qualified to be authors are listed in the author byline. All authors contributed equally to this manuscript.

COMMENTS

Case characteristics

A 25-year-old man with past medical history significant for depression presented to the hospital with two-weeks of nausea and abdominal discomfort accompanied by loose, blood-tinged stools, and tenesmus.

Clinical diagnosis

Jaundice, pruritus, and weight loss.

Differential diagnosis

Primary biliary cholangitis, primary sclerosing cholangitis, graft-vs-host disease, biliary obstruction due to mass.

Laboratory diagnosis

Labs were significant for alkaline phosphatase of 818 U/L, total protein of 4.5 g/dL, albumin of 2.5 g/dL, alanine aminotransferase/aspartate aminotransferase of 46/144 U/L, total bilirubin/direct bilirubin of 6.2/3.9 mg/dL, and INR of 2.23.

Imaging diagnosis

Computerized tomography chest revealed a soft tissue density mass in the left hilar region.

Imaging diagnosis

Computerized tomography chest revealed a soft tissue density mass in the left hilar region.
**Pathological diagnosis**
Cholestatic hepatitis with ductopenia and classical stage II B Hodgkin’s lymphoma.

**Treatment**
Nitrogen mustard and high dose corticosteroids combined with radiation therapy.

**Related reports**
Vanishing bile duct syndrome (VBDS) is a rare disease defined by the loss of intrahepatic bile ducts leading to ductopenia and cholestasis. Early recognition of potential underlying VBDS associated malignancy is critical.

**Term explanation**
VBDS refers to a group of acquired disorders associated with progressive destruction and disappearance of the intra-hepatic bile ducts leading to cholestasis.

**Experiences and lessons**
Early recognition of underlying HL-related VBDS, early aggressive treatment, cholestasis management, and liver transplantation evaluation are paramount to achieve successful outcomes in patients with HL-related VBDS.

**Peer-review**
The paper is well-written.

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