Vanishing Bile Duct Syndrome in a Patient With Recurrent Hodgkin Lymphoma

Olger Nano[a, b, d], Stanislav Ivanov[a, b], Tarun Kapoor[c]

Abstract

Vanishing bile duct syndrome (VBDS) is an acquired syndrome characterized by clinical and laboratory signs of cholestasis with pathologic findings of interlobular bile duct paucity in liver biopsy specimens. VBDS can result from a variety of conditions including infections, autoimmune diseases, adverse drug reactions, and neoplastic processes. Hodgkin lymphoma (HL) is a rare cause of VBDS. The mechanism by which HL leads to VBDS remains unknown. Development of VBDS in patients with HL portends an extremely poor prognosis due to the risk of progression to fulminant hepatic failure. Treatment of the underlying lymphoma has been demonstrated to offer increased probability of recovery from VBDS. The decision to treat and choice of treatment of the underlying lymphoma is often complicated by the hepatic dysfunction characteristic of VBDS. We present the case of a patient who presented with dyspnea and jaundice in the context of recurrent HL and VBDS. We additionally review the literature on HL complicated by VBDS with specific focus on treatment paradigms for management of these patients.

Keywords: Vanishing bile duct syndrome; VBDL; Hodgkin lymphoma; Hepatic failure

Introduction

Vanishing bile duct syndrome (VBDS) is an acquired syndrome which can be seen as a result of numerous underlying causes including genetic diseases (cystic fibrosis, trisomy 17, 18, 21 and Alagille syndrome), infectious etiologies (human immunodeficiency virus, cytomegalovirus, Epstein-Barr virus,

and cryptosporidium infections), autoimmune conditions (sarcoidosis, primary biliary cirrhosis, primary sclerosing cholangitis (PSC), graft-versus-host disease, acute/chronic liver transplant rejection), adverse drug reactions (including weight loss supplements, anti-epileptics, and antibiotics), and neoplastic processes (including both Hodgkin and non-Hodgkin lymphoma as well as histiocytosis X) [1]. VBDS is a clinicopathologic diagnosis characterized by clinical and laboratory signs of cholestasis (jaundice, conjugated bilirubinemia, elevated alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT)) and biopsy-proven paucity of intrahepatic bile ducts [1, 2]. VBDS is a diagnosis of exclusion, requiring a high index of suspicion and exclusion of other common causes of cholestasis as discussed previously.

Hodgkin lymphoma (HL) is a monoclonal lymphoid neoplasm that classically affects young adults with an incidence of 2.6 cases per 100,000 people in the United States [3]. HL commonly arises in cervical, mediastinal, or axillary lymph nodes, and classic biopsy findings show large mononuclear Reed-Sternberg cells intermixed with non-neoplastic inflammatory cells (most often T lymphocytes). Classically, HL patients present with bulky lymphadenopathy; however, patients can present without evidence of palpable adenopathy [3, 4]. Hepatic involvement with HL is relatively common with reported lymphomatous infiltration rates of 5-8% in liver biopsies and as high as 30-70% in autopsy studies in HL patients [5-10]. Presentation with cholestasis as the sole presenting symptom in HL is uncommon (less than 4%) and can be due to lymphomatous infiltration into the liver extrahepatic bile duct, compression from bulky abdominal/periportal lymphadenopathy, or rarely VBDS.

VBDS is an exceedingly unusual complication of HL with approximately 50 cases reported in the literature. HL as a cause of VBDS was first recognized by Hubscher et al in 1993 when they described three patients with severe intrahepatic cholestasis (IC) and liver biopsies consistent with VBDS [11]. Prior to this, similar presentations of patients with jaundice and cholestasis in patients with HL had been reported and were diagnosed as "intrahepatic cholestasis" secondary to HL. The mechanism by which HL leads to VBDS is still not known. Several theories have been proposed including microscopic infiltration of lymphoma cells into the liver, release of cytotoxic cytokines from lymphoma cells leading to direct and/or indirect (e.g., T cell-mediated) destruction of bile duct epithelial cells. The latter theory is favored as biopsy and autopsy specimens have noted absence of lymphoma cell infiltrating the livers of patients with VBDS and HL.
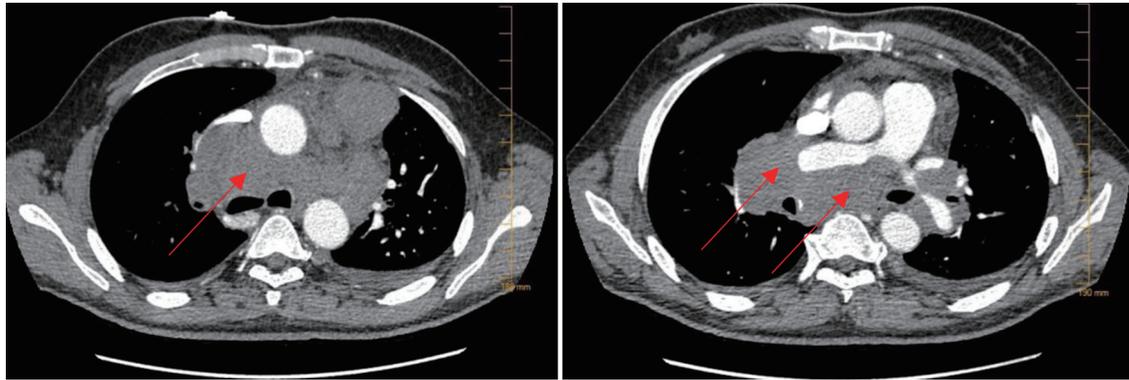
Figure 1. CTA of the lungs. CTA of the lungs on admission showed extensive bulky mediastinal and hilar lymphadenopathy with encasement of the pulmonary artery (arrows). CTA: computed tomography angiography.

Treatment for management of classical HL is based on an anthracycline-based regimens of chemotherapy like adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD). Careful consideration must be given to the choice of therapy used for the management of classical HL, as many of the mainstay agents used are heavily metabolized via the liver. As such, these agents are contraindicated in patients with hepatic dysfunction, including bilirubin > 5 mg/dL. [12, 13]. These considerations pose difficulty in treating patients with HL and VBDS. Management of hyperbilirubinemia with agents like ursodeoxycholic acid and cholestyramine, which has shown promise in other etiologies like primary biliary cirrhosis (PBC) and IC of pregnancy, has had mixed reports when it comes to the management of VBDS, posing yet another hurdle in the management of this condition [14-20].

Case Report

Investigations

A 40-year-old male patient presented to the emergency department with 1 week of worsening shortness of breath, cough, and chest pain. He complained of exertional chest pain and shortness of breath, but denied diaphoresis, palpitations, or headaches. His past medical history was remarkable for hypertension (HTN), alcohol abuse, and HL, which was initially diagnosed 4 years prior to this presentation and was treated with ABVD.

Vitals on admission were notable for temperature of 37.1 °C, blood pressure of 131/73 mm Hg, heart rate of 109 beats per minute, respiratory rate of 18 per minute with oxygen saturation of 99% at room air. Physical exam was remarkable for findings of jaundice, scleral icterus as well as decreased breath sounds over the left lower lobe.

Review of the patient's record was notable for two inpatient admissions 2 months prior to the current presentation. During these admissions the patient was extensively worked up for evidence of recurrent HL. The patient underwent a mediastinoscopy and lymph node biopsy which were negative for evidence of disease. Flow cytometry from the specimens were

inconclusive. The patient developed transaminitis with elevated alanine transaminase (ALT), aspartate aminotransferase (AST) and markedly elevated ALP. The patient underwent evaluation with magnetic resonance cholangiopancreatography (MRCP) which was negative for evidence of obstruction. Subsequent liver biopsy demonstrated no evidence of progressive disease involvement. The patient was lost to follow-up prior to completing outpatient follow-up with endoscopic retrograde cholangiopancreatography (ERCP).

The patient presented once again to the emergency room with complaint of abdominal pain and shortness of breath. Vital signs were stable. Physical examination was once again remarkable for jaundice and scleral icterus. Computed tomography (CT) scan of the abdomen was unremarkable when compared to previous scan obtained at the time of his original diagnosis of HL. The patient was noted to have peri-aortic and abdominal lymph nodes consistent with lymphoma (Figs. 1, 2) Complete blood count on admission were concerning for leukocytosis with elevated white blood count of 47,000/µL with 86% neutrophils and 2% bands, mild anemia with hemoglobin of 8.8 mg/dL, hematocrit of 26.8%, and thrombocytosis with platelet count of 425,000/µL. Comprehensive metabolic panel was significant for hyponatremia with serum sodium of 127, hypochloremia with chloride at 97, alkalemia with bicarbonate of 16. Serum creatinine could not be calculated initially given the severely icteric sample. His ALP significantly increased to 1,876 U/L from 1,045 U/L on last discharge, with relatively stable ALT and AST. His total bilirubin was also markedly elevated to 28.2 mg/dL, with 23.3 mg/dL classified as direct bilirubin. This demonstrated significant change from previous values noted during his last admission, 12.1mg/dL and 10.1mg/dL, respectively. ALP was also noted to be markedly elevated at 1,761 U/L.

Repeat CT of the chest revealed interval development of bilateral pleural effusions along with lymphadenopathy and an increasing pericardial effusion (Fig. 3). Ultrasound-guided thoracentesis was performed yielding 1 L of yellow purulent fluid. His pleural fluid by Light's criteria was consistent with exudative fluid (total protein was 5.8, lactate dehydrogenase (LDH) was 385 (range from our labs is 87 - 241), body fluid protein is 3.1, body fluid LDH was 141. Nevertheless, the fluid collected did not show any significant findings of malignant
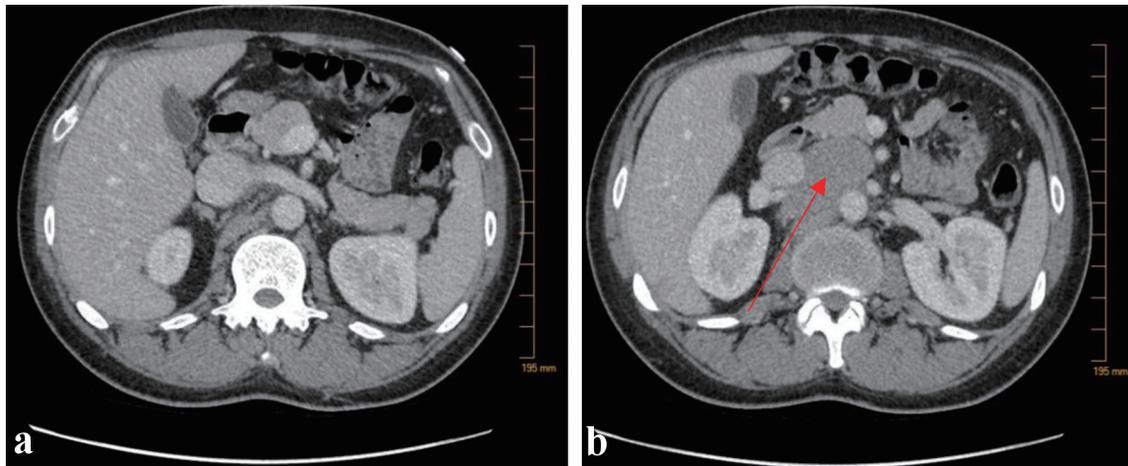
Figure 2. CT abdomen/pelvis with contrast. (a) CT abdomen/pelvis demonstrated a normal appearing liver without evidence of biliary tract dilation. (b) Additional bulky lymphadenopathy was also noted in the aortocaval node region as well as para-diaphragmatic nodes (arrow). CT: computed tomography.

cells.

A new biopsy was performed of the left axillary node which was compared to a biopsy of anterior tracheal mass obtained 4 years prior at the time of HL diagnosis. The results of the biopsy were once again noted to be positive for CD45, CD15, CD30, PAX-5, Fascin and negative for epithelial membrane antigen (EMA) and CD20, consistent with classic HL.

Immunohistology staining showed negative staining for pancytokeratin, synaptophysin, chromogranin, CD56, Mart 1, cytokeratin 7 and cytokeratin 20; but it was diffusely positive for leukocyte common antigen (LCA). Additional immunohistochemical stains were negative for CD15/CD30 with no evidence of Reed-Sternberg cells, PAX 5, CD20 (B cells), cyclin D1, CD23, CD10; it was positive for CD3 (T cells) and CD5. B cell receptor gamma gene rearrangements were also not detected, along with no detection of T cell receptor gamma gene rearrangements and T cell receptor beta gene rearrangements.

Pericardial fluid was not significant enough for pericardiocentesis. The patient's renal function was impaired with creatinine increasing from 1.84 on admission (baseline of 0.6) up to 2.7. This was attributed to be secondary to bile acid nephropathy which was confirmed on urinalysis findings.

Diagnosis

To definitively establish a diagnosis, an ERCP was performed during this hospitalization showing sclerosing cholangitis and atrophy of the intrahepatic bile duct (Fig. 4). Mitochondrial antibody and immunoglobulin G4 (IgG4) were negative. The biopsy collected during ERCP showed portal tracts with mild chronic inflammation with no chronic fibrosis. No metaplastic bile ducts were seen. Of the 13 portal tracts evaluated, none contained significant fibrosis (Fig. 5). No plasma cell infiltrates were seen. Trichrome stain showed no definitive concentric fibrosis but did demonstrate sub-sinusoidal fibrosis. Microscopic findings were consistent with VBDS, which can be seen in patient with HL. Given the constellation of presenting symptoms as well as notable laboratory findings, a diagnosis of VBDS was made with etiology attributed to underlying HL.
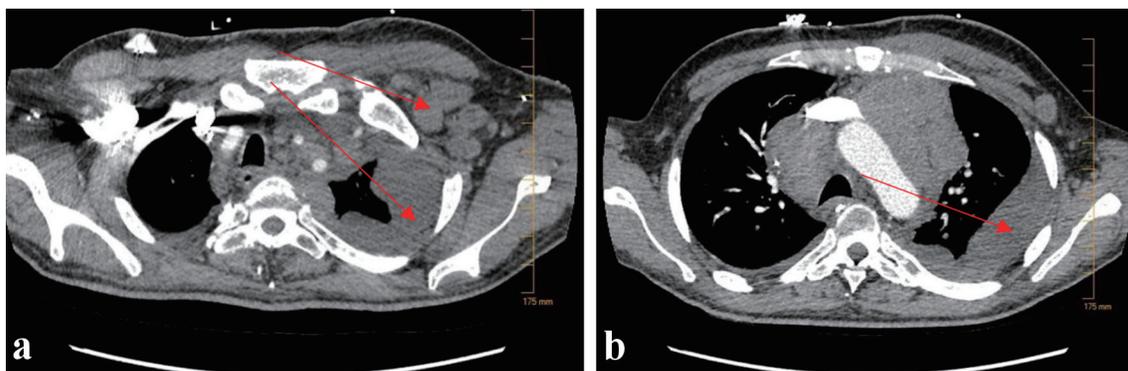

Figure 3. CTA of the lungs upon re-admission 2 months later. Repeat CTA of the lungs showed new, bulky left-sided axillary lymphadenopathy (a) (arrow), as well as extensive, worsening left-sided pleural effusion (a, b) (arrows). CTA: computed tomography angiography.
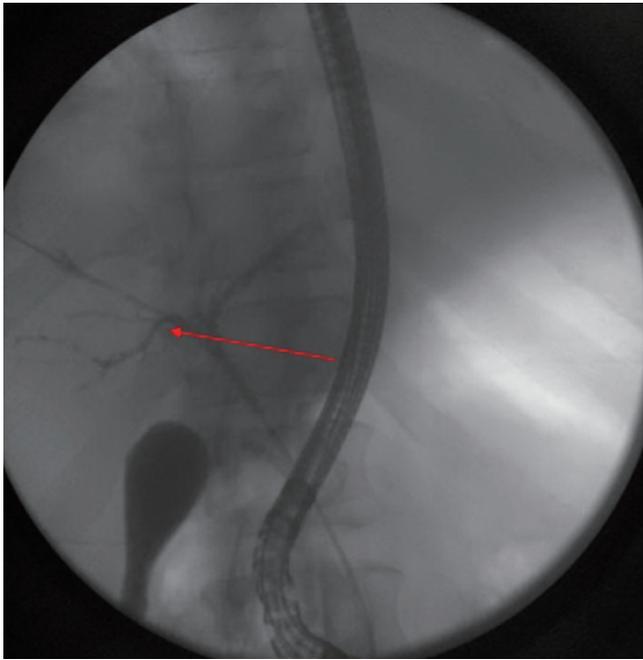
Figure 4. Still image from ERCP study demonstrating failure of contrast penetration through the biliary tree. Findings additionally demonstrate atrophy of intrahepatic ducts with appearance of sclerosing cholangitis (arrow). ERCP: endoscopic retrograde cholangiopancreatography.

Figure 5. Liver biopsy demonstrating absence of interlobular bile duct and hepatocyte injury, consistent with VBDS (arrow). VBDS: vanishing bile duct syndrome.

Treatment

The treatment of VBDS is anchored in the management of the causative process. In the case of our patient, the suspected etiology was recurrence of classical HL. Nonetheless, the treatment proved difficult as many of the active therapies are contraindicated in acute hepatic failure, as their metabolic by-products are hepatically metabolized. A decision was made to start the patient on ursodeoxycholic acid and cholestyramine. As a result of the therapy a minimal improvement in his laboratory values was observed. Subsequently, a pulse of high-dose steroids, dexamethasone 40 mg daily was initiated as means of controlling lymphoma progression and allowing for hepatic recovery. The patient was planned to receive a slow taper over several weeks to allow for hepatic recovery.

Follow-up and outcomes

The patient remained hospitalized for a period but wanted to seek a second opinion. He was discharged in stable clinical conditions and continued his care at a different academic institution.

Discussion

The diagnosis of VBDS in HL patients is challenging, as it is an extremely rare condition. Liver biopsy is required to make the diagnosis. Further, the initial 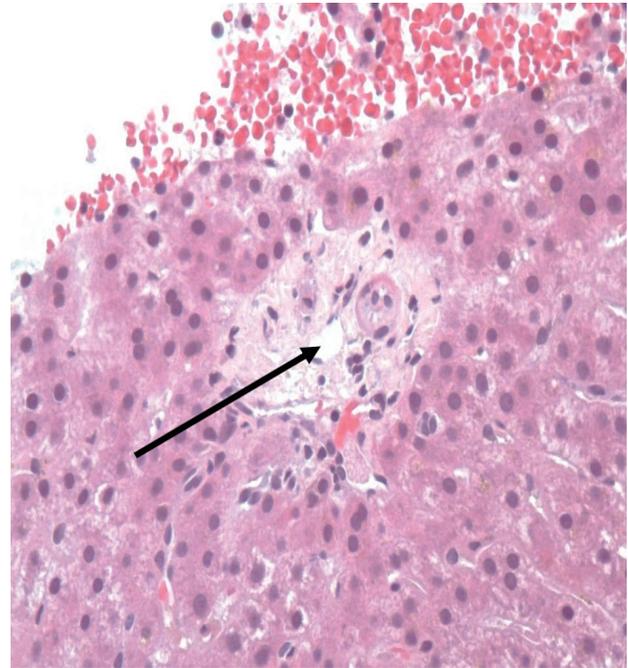presentation of the patient may be nonspecific without overt signs of recurrent lymphoma on physical exam or imaging. Review of reported cases of VBDS in the context of HL demonstrates that the most common presenting signs/symptoms (in order from most common to least common) are jaundice, vague epigastric/abdominal pain, diarrhea/loose stools, weight loss, low-grade/intermittent fevers, pruritus, and less commonly, nausea/vomiting and dark/tea-colored urine. HL defining B-symptoms at or preceding presentation is exceptionally rare and has been reported in a single case study [13]. In several studies, there was no evidence of HL at initial presentation on both exam and imaging studies, and the cause of VBDS was unknown until repeat imaging or physical exam revealed enlarged lymph nodes that were biopsied and ultimately revealed a diagnosis of *de novo* or recurrent HL [18-22]. In one case, the patient was diagnosed with HL after biopsy of lymph nodes that were discovered during screening imaging studies for liver transplantation [20, 22].

VBDS is a diagnosis of exclusion and requires that the clinicians rule out other causes of cholestasis, such as alcoholic or viral cirrhotic liver disease, gall stone disease (e.g., choledocholithiasis/ascending cholangitis), cancers of the biliary tree, and autoimmune diseases (e.g., PBC/PSC), among many others. Additionally, a liver biopsy must be performed with findings that meet strict criteria for the diagnosis of VBDS; mainly, ductopenia defined as a loss of interlobular bile ducts in more than 50% of portal tracts, with at least 11 portal tracts required for analysis (though 20 or more is deemed ideal) [1, 2, 23, 24]. These diagnostic criteria are meant to help distinguish VBDS from IC, which has also been reported as a consequence of HL. IC pathologic findings include cholestasis with inflammatory infiltrates and no significant ductopenia [25]. The rela-

tionship between VBDS and IC is unclear though it has been theorized that IC may either be a precursor to VBDS or that IC and VBDS are at opposite ends of a continuum of the same disease. A relationship between the two entities is supported by case reports of patients with HL and VBDS, where multiple liver biopsies have been taken throughout the disease course. Hallen et al reported the case of a patient that was ultimately diagnosed with VBDS from HL [19]. Initial liver biopsy showed "acute cholestasis and secondary toxic effects" but no ductopenia. A second liver biopsy 3 months later showed acute cholestasis and centrilobular necrosis, but again no loss of bile ducts. Finally, a third biopsy a short time later revealed severe ductopenia, and a diagnosis of VBDS was finally made. Similar findings in other serial biopsy studies have been observed with IC preceding the development of full-fledged VBDS [18].

The cause of ductopenia in patients with VBDS in the context of HL is still unknown. Previously, duct destruction and cholestasis were attributed to direct invasion of the hepatic parenchyma and bile ducts by lymphoma cells, but pathologic examination of specimens from these patients has failed to reveal any evidence of lymphoma infiltration. At present, the leading mechanistic theory is that HL cells secrete a cytokine that is either directly cytotoxic to bile duct epithelium or initiates immune system activation causing autoimmune destruction of bile duct epithelium. There are data suggesting that biliary epithelial cells express major histocompatibility complex (MHC) and intercellular adhesion molecule 1 (ICAM-1) in response to cytokines in liver allografts undergoing rejection, making them increasingly prone to immune-mediated destruction [26]. An autoimmune mechanism is further supported by the fact that biopsies from patients with VBDS have often shown immune infiltrates [1, 13, 22, 27, 28]. Similar cytokine-mediated processes have been suggested as the cause for cholestasis in other cancers, such as Stauffer syndrome with renal cell carcinoma that has been associated with increased interleukin (IL)-6 levels [25, 29].

There are limited data to explain why only a small subset of patients with HL develop VBDS. It has been proposed that this predisposition may be secondary to a host of genetic factors. Bakhit et al published a case report of a patient with HL and VBDS in whom genetic sequencing (via next-generation whole exome sequencing) was performed to look for molecular defects in genes related to bile acid transport or synthesis and identified a defect in the *MST1* gene locus, a locus that is associated with both PSC and inflammatory bowel disease (IBD) [22]. This is even more interesting considering that several patients with VBDS and HL have been co-diagnosed with IBD/colitis [19-22]. This suggests that both VBDS and IBD/colitis in some HL patients may be due to a common paraneoplastic mechanism that is influenced by specific host genetic factors. Moreno et al studied 24 otherwise healthy adults with elevated GGT of unknown cause with liver biopsy [27]. They found that only 62% of their portal tracts had bile ducts. Repeat biopsy on three of these patients years later showed no change, including no worsening. Thus, some authors have theorized that patients that develop VBDS from HL may have baseline cholestasis and are thus more prone to VBDS than other patients with HL with normal bile duct structure/function at baseline [30].

The management of patients with VBDS secondary to HL

is extremely challenging as the cholestasis and liver function abnormalities preclude full-dose first-line chemotherapeutic treatment with ABVD, Stanford V or BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone). Further, liver transplantation is not possible as active Hodgkin disease disqualifies patients for transplant eligibility. Nonetheless, treatment of the underlying HL is the only path forward in the management of patients with VBDS from HL, as left untreated VBDS progresses to biliary cirrhosis, liver failure, and subsequent death. Unfortunately, due to the rarity of the disease, the ideal strategy for treatment of patients with VBDS and HL is not known. As such, clinicians have employed a variety of strategies for treatment of HL in patients with VBDS including definite radiation therapy alone without chemotherapy, single agent chemotherapy with non-hepatically cleared agents (e.g., single agent mustard therapy with mechlorethamine), or modified/alternate regimens where hepatically cleared agents are dose-reduced or omitted (e.g., mechlorethamine, vincristine, procarbazine, and prednisone (MOPP)) [13, 18, 20-22, 28, 30, 31]. In some cases, these therapies have been used initially to try to reduce HL disease burden and alleviate VBDS/cholestasis so that standard treatment regimens (e.g., ABVD) can then be used upon resolution of hyperbilirubinemia [13, 17].

Despite prior beliefs that development of VBDS in patients with HL was irreversible, resolution of hepatic dysfunction and cholestasis has been seen with treatment and remission of the underlying HL [13, 17-19, 28]. Ballonoff et al reviewed all published cases of VBDS and IC and evaluated outcomes of these patients [31]. They found that 1-year overall survival and liver failure-free survival were 43% and 41%, respectively. Further, in the 20 patients with no evidence of residual HL after treatment, 60% achieved liver failure-free survival. While promising, this result reveals that even with treatment and remission of HL, liver failure and death may be unavoidable in a significant portion of patients. On univariate analysis, stage I/II HL, with complete response of HL to treatment, and radiation therapy were associated with statistically significant improved liver failure-free survival. However, it should be noted that this analysis grouped both patients with IC and VBDS together for outcomes. This was justified by the fact that pathologic diagnosis (IC vs. VBDS) was not associated with different outcome on univariate analysis (hazard ratio (HR) 0.81, 95% confidence interval (CI): 0.35 - 1.83); however, most IC cases (12 of 18) were pulled from before 1993 (before VBDS was a known entity), and thus many of these cases of IC may have been VBDS. Therefore, outcomes of patients with VBDS and HL may indeed be even worse than reported.

The treatment of our patient was additionally complicated by the fact that he had new onset and severe renal impairment in addition to marked direct hyperbilirubinemia and hepatic dysfunction. Because of this, treatment with small molecule chemotherapeutics, even modified regimens with reduced dose, was felt unsafe. The mechanism of our patient's renal dysfunction is not known, but several other case reports of HL and VBDS have reported new onset renal dysfunction with reports of acute kidney injury (AKI) of unclear etiology and nephrotic syndrome [13, 22, 25]. Such cases need to be evaluated and treated in academic centers which have the experience and

capability to manage such complex patients.

Conclusions

VBDS is a rare complication of HL that portends a poor prognosis. Without treatment, patients progress to biliary cirrhosis, liver failure, and death. As such, VBDS should remain on the differential diagnosis for patients with HL and unexplained jaundice. The underlying mechanism of VBDS in patients with HL remains unknown but is likely a paraneoplastic phenomenon related to cytokine release from lymphoma cells. Exclusion of other cholestatic processes and liver biopsy are required for the diagnosis of VBDS. Treatment of patients with VBDS in the context of HL should focus on treating the underlying HL to prevent worsening liver damage and hepatic failure. While some patients experience complete recovery of liver function with treatment, a significant proportion who receive treatment and achieve HL remission have persistent liver abnormality and may still progress to liver failure and death. Early diagnosis and treatment of underlying HL are likely crucial to improving outcomes in these patients.

Learning points

VBDS is a known complication of HL.

Recognition of VBDS requires a high index of clinical suspicion.

Diagnosis of VBDS is based on clinical presentation, as well as radiologic and pathologic evidence of this phenomenon.

Treatment includes management of the underlying HL which can be complicated by concurrent presence of hepatic failure. Supportive therapy including use of high-dose steroids and ursodeoxycholic acid are appropriate lines of therapy.

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Conflict of Interest

None to declare.

Informed Consent

Data used in this clinical case report were deidentified. Permission was granted to use for the data in educational publications.

Author Contributions

Olger Nano MD, FACP, as primary author of publication, assembled relevant clinical data as well as literature review, provided interpretation of clinical data and summary of relevant information in the literature. Stanislav Ivanov, MD, MPH, as editor, provided editing and formatting of publication. Taroon Kapoor, as editor, provided editing and formatting of publication.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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