Hodgkin lymphoma associated vanishing bile duct syndrome treated successfully with a brentuximab based regimen

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SUMMARY
We report a combination therapy to successfully treat a patient with Hodgkin’s lymphoma complicated by vanishing bile duct syndrome. Our patient was in his 20s and presented with jaundice, emesis, B symptoms and diffuse lymphadenopathy along with cholestatic liver injury prompting a liver biopsy, which revealed this diagnosis, after the exclusion of other aetiologies. Our treatment regimen incorporated brentuximab along with other more conventional agents which attempted to maximise therapeutic efficacy while minimising the consequences of hepatotoxicity on the treatment protocol. Although this patient’s treatment course was complicated because of neutropenic infections, the patient achieved a complete metabolic response and is now more than 1 year off therapy.

BACKGROUND
Cholestatic liver injury is rarely seen on the initial presentation of a patient with classic Hodgkin’s lymphoma (cHL), occurring in less than 4% of cases.1 When present, it can be due to a variety of malignancy related causes. These include direct malignant invasion of liver parenchyma, bile obstruction due to tumour mass effect, viral reactivation enabled by malignancy mediated immunodeficiency, a malignancy associated hemophagocytic process and finally a paraneoplastic phenomenon. There are also a variety of more common causes of liver injury that occur in this population such as choledocholithiasis, drug-induced liver injury and a new viral hepatotropic infection. Thus, paraneoplastic phenomena represent a very rare cause of cholestatic liver injury within this group and can be separated into idiopathic cholestasis and vanishing bile duct syndrome (VBDS) based on the presence or absence of a characteristic amount of intrahepatic small bile destruction seen on liver biopsy.2 VBDS generally carries a poor prognosis.3 How best to treat a patient with cHL and VBDS is unclear. We present a case of VBDS diagnosed in a patient presenting with cHL. We employed a treatment regimen designed to minimise hepatotoxicity using a variation of brentuximab with doxorubicin, vincristine, etoposide, prednisone and cyclophosphamide (AVE-PC) which resulted in a complete metabolic response for our patient and significant improvement in his cholestasis.

CASE PRESENTATION
A male patient in his 20s presented with 3 days of jaundice, abdominal pain and nausea in the setting of 6 months of intermittent fevers and 10 kg of unintentional weight loss. An outpatient workup had been initiated for possible lymphoma with plans for a lymph node biopsy after a recent hospitalisation at another hospital for syncope in which the patient was noted to have bulky, diffuse adenopathy on imaging and a moderate, mostly lymphocytic pericardial effusion that was drained. The patient was treated with four doses of amoxicillin–clavulanate at this time, 3 months before presentation. Unfortunately, due to a diagnosis of COVID-19, an outpatient lymph node biopsy had been delayed. The patient also had a recent plain radiograph which showed a lytic lesion in his proximal femur which was performed for evaluation of approximately 1 year of right hip pain. The patient had no other medical history, significant medication exposures and no recent travel outside the northwestern USA.

Physical examination at the time of admission was most notable for jaundice, scleral icterus and diffuse palpable lymphadenopathy. Laboratory workup demonstrated a leucocytosis (15.0 x 109/L) and elevated inflammatory markers (erythrocyte sedimentation rate (ESR) 101 mm/hr and C-reactive protein (CRP) 3.4 mg/dL). Liver tests were notable for a total bilirubin of 10.9 mg/dL with a direct component of 8.5 mg/dL, alkaline phosphatase of 941 U/L, and aspartate and alanine aminotransferase levels of 102 and 132 U/L, respectively.

INVESTIGATIONS
Initial CT revealed diffuse lymphadenopathy, pulmonary nodules, new hepatomegaly and splenic hypodensities. No obstruction or gall bladder distention was noted on ultrasonography of the abdomen or on magnetic resonance cholangiopancreatography. A viral hepatitis panel, Cytomegalovirus (CMV), Epstein-Barr virus (EBV), Alpha-1 antitrypsin (A1AT), antinuclear antibody (ANA), antimitochondrial antibody (AMA), anti-smooth muscle antibody (ASMA), uric acid level and a ferritin level were all unremarkable. A cervical lymph node biopsy and medullary femur biopsy confirmed nodular sclerosing classic Hodgkin lymphoma. Microscopic findings included sclerotic bands causing lymph node effacement and large, atypical, multinucleated cells with prominent eosinophilic nuclei (figure 1). Immunohistochemical
staining demonstrated positivity to CD15 and CD30 with negative staining for CD45. Given the diffuse, bulky disease and likely pulmonary, bony and splenic involvement, the patient was classified according to Ann Arbour classification as stage IVb disease.

A liver biopsy showed portal tracts inflammation with focal small bile duct destruction and dropout while sparing medium to large bile ducts consistent with acute cholangitis with marked cholestasis (figure 2). Fibrosis stage was F0 on biopsy. CK7 stain confirmed small bile duct obliteration (figure 3). No Reed–Sternberg cells were seen within the liver biopsy. In the absence of lymphoproliferative infiltration of the liver, the pathology was highly suggestive of VBDS given cholestasis and ductopenia.

**TREATMENT**

The patient was started on symptomatic treatment for pruritus with colestipol and diphenhydramine while awaiting biopsy results. Additionally, ursodeoxycholic acid was initiated after imaging was negative for obstructive pathology. A prednisolone dose of 35 mg two times per day was given for 7 days initially in the hospital. Despite pretreatment with ursodeoxycholic acid and prednisolone, the bilirubin rose to 19.6 mg/dL with a direct bilirubin of >10 mg/dL. Therapy with two cycles of brentuximab vedotin (dose reduced for decreased liver function to 1.2 mg/kg) and cyclophosphamide with prednisone (BV-PC) was initiated. Brentuximab was given on day 1, cyclophosphamide on day 5 and both again on day 17. Total bilirubin peaked at 21.7 mg/dL a few days after the second dose of BV-PC then down trended to 12 mg/dL, at which point the patient was started on a modified brentuximab vedotin, doxorubicin, vincristine, etoposide, prednisone and cyclophosphamide (Bv-AVE-PC) protocol. Prednisolone 35 mg was also given two times per day for 7 days at the start of cycles 1–3. This was the same as used in the ongoing Children’s Oncology Group Phase 3 study AHOD 1331 though it was 50% dose reduced for decreased liver function for cycle 1 and then increased to 75% for cycles 2–5.

**OUTCOME AND FOLLOW-UP**

The patient’s bilirubin slowly down trended over the course of treatment (figure 4).

The patient’s treatment course was complicated by multiple admissions for neutropenic infections including neutropenic fever and both *Streptococcus mitis* bacteria and *Clostridium difficile* colitis during cycle 1 of Bv-AVE-PC. The treatment course was complicated by multiple admissions for neutropenic fever (due to *S. mitis*, *Klebsiella pneumoniae* and twice without identifiable pathogen), which occurred once per cycle. Additionally, during an admission for neutropenic fever during cycle 3 patient was found to have pneumonitis treated with high-dose steroids. The most recent follow-up was documented—19 months after original admission to our facility and 12 months after completion of chemotherapy which showed a bilirubin that has now down trended to 1.7 mg/dL and a continued complete metabolic response on imaging.

**DISCUSSION**

VBDS refers loosely to a group of acquired disorders involving the destruction and disappearance of intrahepatic bile ducts and ultimately cholestasis as a result. It has been distinguished from intrahepatic cholestasis by the identification of ductopenia >50% on an adequate biopsy specimen showing at least 11 portal...
It was first described in association with cHL by Hubser et al in 1993, but has also been associated with viral infections, autoimmune aetiologies and several medications. Cholestatic liver injury is a rare presentation for cHL with VBDS being even less common with only 37 cases reported since 1993. Several cases of paraneoplastic idiopathic cholestasis without evidence of ductopenia on biopsy have also been reported. These may represent an earlier manifestation of the same clinical entity. While specific pathogenic mechanisms are not well understood, theories include antibody mediated destruction, direct cytotoxic actions of T cells, and damage of bile epithelium due to high levels of cytokines resulting in apoptosis of small bile duct epithelial cells. VBDS can be caused by a variety of drugs as well to include amoxicillin–clavulanate though given exposure to have died of liver related complications. In contrast, since first described in 1993, 37 cases of VBDS associated cHL have been reported in the English medical literature. Including our case, of the cases with known outcomes, 16 of 35 resulted in short interval death with the majority appearing to have died of liver related complications. In contrast, since 2019 only 3 of 11 cases ended in death. Given the lack of many reported cases, it is difficult to determine if the improvement in mortality is attributable to improvement in treatment outcomes. Most prior reports describe therapy attempting to target the underlying malignancy as fully as possible while balancing the risk of drug related hepatotoxicity. Prior to this report, only five reported cases employed brentuximab vedotin in the treatment of cHL with VBDS. Fong et al employed it as an adjunctive therapy to a cyclophosphamide-based regimen starting in cycle 4 in a case of stage III cHL. Gupta et al described using brentuximab as a single agent initially for two patients with VBDS and cHL until serum bilirubin fell below 5 mg/dL, which took about 2–5 months followed by five cycles of doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine (ABVD) with complete remission in those two patients. Ishitsuka et al describe using brentuximab as salvage therapy after several other regimens for a patient who was originally felt to have anaplastic large cell lymphoma with possible liver involvement but ultimately reclassified as cHL with VBDS. A partial metabolic response was achieved with five cycles of the dose reduced to 1.2 mg/kg and then stable disease was seen with another five cycles of the regular dose of 1.8 mg/kg though the patient ultimately had progression of disease on this regimen. Finally, Papakonstantinou et al describe also treating a patient with stage IIIb cHL with dose reduced brentuximab as monotherapy for 2 weeks and saw a dramatic improvement in liver function with this allowing initiation of full dose chemotherapy thereafter.

Our main goal in selecting the therapy for this patient was to maximise the chance of cure while minimising treatment related morbidity. The protocol we used, AHOD1331, had shown that the addition of brentuximab to the chemotherapy backbone containing doxorubicin, vincristine, etoposide, cyclophosphamide and prednisone (ABVE-PC) results in an outstanding 3-year event-free survival (EFS) of 92%. However, because of this patient’s known hepatic dysfunction, we also wanted to minimise the morbidity of hepatotoxicity while maximising agents with known activity treating cHL. Given its efficacy in cholestasis, we initially treated it with ursodeoxycholic acid. Despite starting with a similar steroid regimen to the study by Scalabrini et al, the tests performed on liver showed worse results. This may suggest a different phenotype or perhaps a later stage of disease in our patient. We, therefore, employed a graded approach to therapy, similar to that used by Fong et al. Brentuximab was used at an earlier stage based on its targeted activity against malignant Hodgkin cells. Additionally, brentuximab is associated with a similar hepatotoxicity profile as well as favourable outcomes in recent trials, including the AHOD1331 trial. While a single case of severe liver injury was reported after seven cycles of full dose brentuximab vedotin in 2019, the incidence of hepatotoxicity was low, likely between 0.61% and 1.4%. Additionally, it has been successfully employed in several other cases of VBDS. We also avoided vincristine and doxorubicin which would have obvious toxicity due to its metabolism by the liver. The addition of brentuximab and cyclophosphamide to prednisone for two cycles provided substantial improvement in bilirubin to approximately 50% of peak levels. The modified Bv-AVE-PC protocol, as used in AHOD 1331, was then employed due to its favourable outcomes with adjusted chemotherapy doses based on hepatotoxicity.

It should be noted that despite an initial 50% dose reduction for cycle 1 and 75% dose for cycles 2–5, our patient’s treatment course certainly had a higher than expected rate of neutropenic fever admissions. Each involved an absolute neutrophil count <500/µL reflecting National Cancer Institute grade 4 events. This is indeed higher than what is typically seen with this regimen and higher than has been reported recently. Although we realised that the initial dose reduction of 50% was inadequate to account for the reduced hepatic function in this patient, we also did not want to undertreat the patient’s lymphoma and thus chose to maintain the intensity of treatment and escalated therapy with improving liver functions and used both granulocyte-colony stimulating factor (G-CSF) and polyethylene glycol conjugated granulocyte colony-stimulating factor (PEG-G-CSF) to minimise the period of neutropenia. Because the patient’s period of neutropenia was not prolonged, we maintained the intensity of therapy. Nevertheless, further dose reductions could have likely been used to decrease the infectious complications.

In summary, we present a case of VBDS due to cHL successfully treated with a modified protocol involving two cycles of Bv-PC before the initiation of five cycles of Bv-AVE-PC which ultimately achieved a complete metabolic response for our patient. This case highlights the importance of recognition and early treatment of a rare complication of cHL by first excluding a variety of more common causes of liver injury and obtaining a liver biopsy if clinical suspicion is high. Our case also suggests that pre-treatment cycles of Bv-PC can be used to effectively reduce serum bilirubin before initiation of more standard chemotherapy protocols if not responsive to ursodiol and prednisone.

Figure 4 Patient’s liver associated enzymes and bilirubin throughout treatment course. Figure generated by Robert Weishar.
alone. Many studies since its original approval in 2011 have indicated that brentuximab can potentially improve outcomes when added to a variety of chemotherapy regimens.24 We suggest that Bv-C followed by Bv-AVE-PC may provide effective treatment for patients with advanced cHL associated with VBDS to minimize further liver injury while effectively treating the underlying malignancy.

Learning points

► Vanishing bile duct syndrome (VBDS) is a rare and serious phenomenon involving the destruction of the intrahepatic bile duct that can sometimes be associated with classic Hodgkin’s Lymphoma (cHL).

► Extensive evaluation is initially warranted to rule out other causes of hepatic injury in any patient presenting with likely lymphoma and hepatic dysfunction, but a liver biopsy may be needed and show pathologic small bile duct destruction which is concerning for this phenomenon.

► If this is discovered, a thorough review for any signs of malignancy (cHL in particular) is important.

► For VBDS in the setting of cHL, aggressive treatment of the underlying malignancy is paramount and brentuximab Ventolin may provide an effective option for early chemotherapy without profound liver toxicity when appropriately dose reduced as is suggested by our patient and a few other cases.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

REFERENCES


