CASE REPORT

# Acute liver failure secondary to ABVD use

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## SUMMARY

Hodgkin's lymphoma (HL) is a type of cancer originating in the lymph nodes. The preferred therapy for advanced HL is a combination of chemotherapies including doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD). ABVD has been standard therapy for advanced HL. It is generally considered as safe and rarely has been reported to cause acute liver failure. We present a case of 79-year-old woman with HL, who developed acute liver failure secondary to first cycle of ABVD chemotherapy.

## BACKGROUND

Hodgkin's lymphoma (HL), also referred to as Hodgkin's disease, is a type of cancer originating in the lymph nodes and characterised by the presence of malignant Reed-Sternberg cells in a reactive cellular background. While HL begins in the lymph nodes, it often spreads to nearby tissues in an organised way.[1] On diagnosis, a patient with the HL usually undergoes a particular chemotherapy regimen based on the disease stage. The preferred therapy for patients with advanced HL is a combination of chemotherapies including doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD). For the past few decades, ABVD has been the standard of care in treating advanced HL, and based on how the disease responds, the therapy is continued for six, or less often eight, cycles (one cycles includes two administrations).[2–5] A commonly reported chemotherapy side effect is mild, transient transaminase elevation. However, ABVD, while cytotoxic to cancerous cells, rarely leads to acute liver failure. Herein, we present the case of 79-year-old woman with HL. After the first dose (first cycle) of ABVD therapy, the patient presented with a fever, abdominal pain and syncope and subsequently developed acute liver failure. After N-acetyl cysteine (NAC) and saline infusion, a relatively rapid recovery was achieved.

## CASE PRESENTATION

A 79-year-old Caucasian female who presented to the emergency department with unwitnessed syncope at home after receiving her first cycle of chemotherapy with ABVD regimen for classical HL. Her chemotherapy completed around noon that day, and she went home at 13:00, felt weak, cold and light headed. She lived alone, her neighbour went to check her 3 hours later, found her slumped over in a chair with vomits around her mouth. Patient could not recall what happened in between. Patient's medical history was significant for left breast low grade invasive ductal carcinoma (T1bN0M0) diagnosed in 2007, status post left partial mastectomy and sentinel node resection, oestrogen receptor/progesterone receptor positive, human epidermal growth factor receptor-2/neu receptors negative for which she was treated with letrozole until 2011 without radiation or adjuvant chemotherapy. In October 2017, she was found to have cervical adenopathy during a family doctor visit after fall, further CT imaging revealing extensive metabolically active lymphadenopathy in the neck, chest, abdomen and pelvis consistent with lymphoma (Deauville 5) with subsequent lymph node biopsy illustrating atypical cellularity and bone marrow pathology consistent with classical nodular sclerosing HL Stage III, International Prognostic Score 3.

Patient was normotensive and haemodynamically stable when brought to the emergency room. She was treated with 2 L of saline intravenous infusion. Initial laboratories were noted to have significantly elevated transaminases (alanine aminotransferase (ALT) 980 U/L, aspartate aminotransferase (AST) 2955 U/L, alkaline phosphatase 126 U/L, bilirubin 2.6 mg/dL), lactic acidosis (5.3 mmol/L), high anion gap metabolic acidosis (anion gap 19) and coagulopathy (international normalised ratio 2.26) with thrombocytopenia. Of note, her liver function test was completely normal day before her chemotherapy was given. Patient did have detectable acetaminophen level of 3.3 $\mu$g/mL and was started on NAC.

## INVESTIGATIONS

A report on the investigation is shown in table 1.

## TREATMENT

High anion gap metabolic acidosis and elevated uric acid hinted at the clear potential of developing tumour lysis syndrome (TLS) and she was initiated on maintenance fluid and allopurinol for TLS prophylaxis. Acute thrombocytopenia in the setting of acute liver failure was concerning for consumption, rather than bone marrow suppression related to chemotherapy; for which disseminated intravascular coagulation (DIC) workup was completed, and with normal fibrinogen level DIC was less likely. Her 6 days of hospital course consisted of supportive care and close monitoring of her hepatic function, which improved with fluid resuscitation and NAC infusion. She underwent liver ultrasound which did not show thromboses or any flow abnormalities. Her infectious workup was completely negative. CT imaging of head and brain showed no acute finding to explain her syncope. Telemetry was unremarkable for arrhythmias. She developed



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**Table 1** Investigation reports

| | Day prior | First day of admission | Second day of admission | 14th day |
|---|---|---|---|---|
| White cell count (4.5–11 $10^9$/L) | 9.47 | 9.12 | 10.32 | 51.94 |
| Haemoglobin (13–17 g/dL) | 9.9 | 9 | 9.1 | 9.4 |
| Haematocrit (41%–51%) | 30.5 | 29 | 29.7 | 28.2 |
| Platelets (150–450 $10^9$/L) | 307 | 232 | 99 | 356 |
| Blood urea nitrogen (8–20 mg/dL) | | 23 | 31 | 23 |
| Cr (0.7–1.3 mg/dL) | | 0.8 | 1.2 | 0.7 |
| $Na^+$ (136–145 meq/L) | | 136 | 137 | 133 |
| $K^+$ (3.5–5.0 meq/L) | | 4.5 | 4.8 | 3.2 |
| Anion gap (7–15 mmol/L) | | 14 | 19 | 14 |
| Phosphorus (2.5–4.5 mg/dL) | | | 4.3 | 1.4 |
| Alkaline phosphatase (44–147 IU/L) | | 105 | 126 | 172 |
| Alanine aminotransferase (7–35 IU/L) | | 24 | 980 | 90 |
| Aspartate aminotransferase (7–40 IU/L) | | 30 | 2955 | 56 |
| Prothrombin time/international normalised ratio | 1.15 | | 2.26 | |
| Uric acid (2.4–6 mg/dL) | | | 7.9 | |
| Lactic acid (0.4–2.5 mmol/L) | | | 5.3 | |

anaemia without overt bleeding for which she required 1 unit of packed red blood cell transfusion. The patient declined liver biopsy to further clarify the aetiology of her acute liver failure. Given liver failure developed acutely after she received ABVD chemotherapy, with normal liver function test 1 day prior to chemotherapy, we felt that ABVD chemotherapy was the culprit for her liver failure. Though with her presentation of syncope, shock liver was also under the differential diagnosis, but given her normal blood pressure and relatively normal kidney function at the presentation, shock liver was less likely. We further suspected dacarbazine was the causative agent for her acute liver failure; however, a synergistic adverse drug reaction cannot be excluded.

## OUTCOME AND FOLLOW-UP

During her next visit, she was started on brentuximab vedotin intravenous every 3 weeks. She has been tolerating brentuximab and she will receive a total of six cycles of brentuximab.

## DISCUSSION

Although initially developed to treat diseases resistant to mechlorethamine, vincristine, procarbazine and prednisone, ABVD is now the standard chemotherapy treatment for patients with HL.[6] Typically, administration of ABVD is repeated every 14 days in 28 day cycles, up to a maximum of six cycles (most common). The response is regularly monitored during treatment using imaging techniques, and once the optimal response is achieved, two further chemotherapy cycles are completed. Therefore, the total chemotherapy duration usually ranges from 24 to 32 weeks. Common ABVD-related toxicities are nausea, vomiting and neutropaenia[7]; however, the use of potent antiemetic agents has significantly reduced the severity of side effects. Less frequent toxicities include severe infections, occurring in 2% of patients, anaemia in 5% and thrombocytopenia in 3%.[7 8]

Throughout systemic chemotherapy treatment, mild and transient elevation of serum aminotransferase levels is typical. Combining different antineoplastic protocols can lead to acute liver failure; however, the specific role of ABVD remains unclear. An extensive review of the literature on hepatotoxicity secondary to ABVD reveals that transient elevation of liver enzymes in liver function tests is often observed with bleomycin, doxorubicin, vincristine and ABVD administration.[9] Doxorubicin is mainly metabolised by the liver and 40% of patients receiving doxorubicin monotherapy show mildly elevated serum aminotransferase; however, patients are usually asymptomatic and transient, and elevated serum aminotransferase levels tend to resolve regardless of the continued doxorubicin.[10–12] Delayed clearance of doxorubicin was observed in patients with cholestasis.

A low incidence of liver dysfunction is generally reported in patients receiving bleomycin therapy.[13 14] Based on a review of more than 1000 treated patients, hepatotoxicity tends to be inconsistent and a specific pattern of hepatic injury related to the use of bleomycin has yet to be described.[13] In 10%–40% of patients, bleomycin combined with other chemotherapy drugs was linked to serum liver enzyme elevation and in 1%–7% of patients, levels five times greater than the upper limit of normal levels were observed depending on the dosage and additional drugs administered.[13] Simply associating transaminitis with bleomycin treatment is unreasonable in most cases since a patient is often exposed to other possibly hepatotoxic agents. In rare cases, liver damage is clearly evident in patients treated with bleomycin; however, the onset and injury pattern vary considerably and are usually associated with sinusoidal obstruction syndrome or reactivation of hepatitis B. Other protocols using bleomycin to treat HL have resulted in vanishing bile duct syndrome; however, this type of liver injury also occurs in untreated patients with HL, with a number of incidences occurring prior to the diagnosis of HL.[14–17]

The clinical presentation of acute hepatic injury associated with dacarbazine (DTIC) has a distinct progression. During the first course of therapy, a number of cases have reported mild nausea and fever along with peripheral eosinophilia. While some characteristics of DTIC-induced hepatic injury are similar to those seen in acute ischaemic necrosis due to shock or hepatic infarction, the direct cause is, in fact, believed to be acute sinusoidal obstruction syndrome.[18–21] Coagulopathy is normally observed throughout the early treatment stages accompanied by an increase in ALT and lactate dehydrogenase (LDH) levels, indicating acute hepatic necrosis (quickly reversed in non-fatal cases). Bilirubin, however, is not elevated until later stages of progressive hepatic failure (ascites, hepatic encephalopathy).[18 19]

Hepatic injury typically presents suddenly during the second course of therapy, accompanied by the rapid onset of fever, abdominal pain and subsequent cardiac circulatory collapse, as well as a significant increase in serum aminotransferase and LDH levels.[18 19] In this report, our patient presented with a profile similar to DTIC-induced acute hepatic injury, characterised by the acute onset of fever, abdominal pain, cardiovascular collapse and subsequent elevations in ALT, AST and LDH levels, in addition to coagulopathy. With supportive care and NAC infusion, symptoms rapidly subsided. The only dissimilarity to previous reports is that our patient developed acute hepatic injury on the very first day of chemotherapy (first ABVD cycle).

Microscopic examination of a liver that has undergone DTIC-induced failure shows centrilobular necrosis, infiltration by eosinophils and other inflammatory cells and thrombosis throughout the small and large hepatic veins.[20] N-acetylcyteine has the antioxidant, anti-inflammatory and vasodilatory effects.[22 23] These effects lead to improvement of oxygen delivery

to tissue and subsequently improving systemic haemodynamic. Various studies have discussed the benefits of NAC in the treatment of acetaminophen induced acute liver failure. Despite significant limitations, a recent prospective randomised case control trial conducted in 2017 showed NAC along with conventional treatment benefitted the patient with non-acetaminophen induced acute liver failure.[24] The patient in this report declined a liver biopsy, and therefore it was not possible to confirm the particular cause of acute liver failure. Liver toxicities as a result of ABVD therapy can be effectively treated using supportive management with NAC and the administration of intravenous fluid. During the first 3 days of hospitalisation, our patient was treated with NAC, normal saline hydration and allopurinol. No existing parenchymal liver disease was present that could have led to a worsening of symptoms. Moreover, no reactivation of underlying hepatitis B or C occurred, as indicated by negative serology results. Peripheral eosinophilia, suggestive of a hypersensitivity reaction, was unlikely; however, the patient refused a liver biopsy, which may help to explain the exact aetiology. The most noteworthy aspect of this case is the rapid onset of acute liver failure just a few hours after the first ABVD cycle, with symptoms including fever, abdominal pain and loss of consciousness. Although recognised as a relatively safe chemotherapy regimen, ABVD chemotherapy is not without risks, and while this may have been an exceptional incident, patients should be appropriately supervised during the first 24 hours after initial administration of ABVD.

## Learning points

- While generally rare, acute liver failure can occur with doxorubicin, bleomycin, vinblastine and darcarbazine (ABVD) chemotherapy. In such cases, the initial presentation may be in the form of cardiovascular collapse. Therefore, patients should receive 24 hours surveillance while receiving ABVD chemotherapy, particularly throughout the initial phase to ensure no acute adverse reaction.
- In non-acetaminophen-induced acute liver failure, supportive care with N-acetyl cysteine may aid in the quick recovery of liver function.

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## Unexpected outcome (positive or negative) including adverse drug reactions