

CASE REPORT

Acute liver failure due to hepatitis B virus reactivation induced by doxorubicin and cyclophosphamide chemotherapy for adjuvant treatment of breast cancer: A case report

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Abstract

Acute liver failure developed in a 48-year-old woman within days after she received adjuvant chemotherapy for breast cancer. On arrival at ED, she had severe encephalopathy and jaundice. Serum analyses demonstrated coagulopathy and markedly increased transaminases. She was admitted to the ICU for supportive treatment but died several days later.

KEYWORDS

acute, adjuvant, case reports, chemotherapy, hepatic encephalopathy, hepatitis B virus, jaundice, liver failure

1 | INTRODUCTION

Acute liver failure (ALF) is a rare syndrome of acute liver dysfunctions in a patient without underlying chronic liver disease.¹ It occurs over days to weeks with a duration of illness <26 weeks. The syndrome is characterized by severe coagulopathy (prothrombin time prolonged by 4–6 s and INR >1.5), jaundice, and hepatic encephalopathy with or without cerebral edema.¹ It is typically associated with acetaminophen overdose; 45%–60% of ALF cases in the United States and the United Kingdom.¹ Other causes include viral and autoimmune hepatitis, malignant infiltration of the liver, ischemic causes, pregnancy-related conditions, idiosyncratic drug reactions, and, in some cases, unknown etiology.² ALF rarely develops in patients with acute hepatitis B virus (HBV) infection (0.4%–4%).¹ In particular, ALF needs to be considered in HBsAg-positive or anti-HBc-positive patients undergoing immunosuppressive or cytotoxic therapy as HBV can reactivate.³

HBV reactivation (HBVr) is defined as a ≥ 2 log (100-fold) increase in HBV DNA compared to the baseline level; or HBV DNA ≥ 3 log (1000) IU/ml in a patient with previously undetectable level; or HBV DNA ≥ 4 log (10,000) IU/ml if the baseline level is not available.⁴ The mainstay of ALF management remains supportive treatment in critical care settings.^{2,3} Nevertheless, ALF due to HBV is associated with 60%–80% mortality rate and often higher if HBV reactivates,¹ and hence, the patient may require an urgent liver transplant. Here, we report a case of ALF due to HBVr induced by doxorubicin and cyclophosphamide chemotherapy for adjuvant treatment of breast cancer. We appraise the clinical, laboratory, and imaging findings; discuss treatment and prognosis; and review the available literature.

2 | CASE PRESENTATION

A 48-year-old woman, known to have an inactive HBsAg carrier state, was brought to the emergency

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department (ED) because of stupor. Six months earlier, the patient had received a diagnosis of breast cancer with no history of central nervous system involvement or co-existing conditions. She underwent surgical resection, followed by four cycles of adjuvant chemotherapy with doxorubicin (60 mg/m² IV) and cyclophosphamide (600 mg/m² IV) every 14 days. Prophylactic entecavir 0.5 mg orally once a day was initiated from day 1 of the first cycle of chemotherapy for preventing HBVr. The fourth cycle of chemotherapy was administered 3 weeks before her presentation to the ED. On arrival, she was stupor and had severe jaundice. No signs of headache, vomiting, focal deficits, agitation, hallucination, pain, changes in bowel or bladder function, or shortness of breath were noticed. No trauma or seizure was observed. She did not use alcohol or illicit drugs. Vital signs, including temperature, were normal. Her physical examination was notable only for disorientation and difficulty in finding words and unremarkable for focal neurologic abnormalities or signs of chronic liver disease (no splenomegaly, ascites, shrinking liver volume, or peripheral edema). An emergency abdominal ultrasonography showed no evidence of liver cirrhosis or biliary obstruction. Computed tomography (CT) of the brain showed features of cerebral edema. Her initial investigations are shown in Table 1. Serum analyses demonstrated severe coagulopathy (PT 49.8 s, INR 3.6), markedly increased transaminases (ALT = 3716 Unit/L and AST = 3972 Unit/L), moderately increased alkaline phosphatase (223 Unit/L) and total bilirubin (10 mg/dl)

levels, and metabolic acidosis. Viral hepatitis B serology showed positive hepatitis B surface antigen (HBsAg), negative hepatitis B e antigen (HBeAg), and a high level of HBV DNA (50,000 IU/ml).

Her clinical presentation and history suggested ALF due to HBVr induced by doxorubicin and cyclophosphamide chemotherapy for adjuvant treatment of breast cancer. ALF is a rare, life-threatening condition of rapidly deteriorating liver function. The syndrome is reported to be rarely associated with acute HBV. Its clinical presentation is characterized by severe acute liver injury defined as liver damage markers (elevated serum transaminases) and impaired liver function (jaundice and INR >1.5), preceding clinical encephalopathy with or without cerebral edema. Because of severe encephalopathy (Grades 3–4), the patient was intubated for airway protection and admitted to the intensive care unit (ICU). Supportive treatment was initiated consisting of IV fluids including dextrose 10% for volume resuscitation. The patient was given the nucleoside analog entecavir orally via nasogastric tube (NGT) for hepatitis B viremia, prophylactic intravenous (IV) antibiotics for preventing sepsis, IV Mannitol for elevated intracranial pressure, prophylaxis for gastrointestinal bleeding with IV Omeprazole, IV Vitamin K, lactulose as an enema, and orally via NGT for encephalopathy, and high-volume plasma exchange with fresh frozen plasma. The patient was referred to a specialized liver transplant center, but the syndrome progressed, and she died several days later.

TABLE 1 Results of laboratory studies

Lab	Value	Reference range
Hematology		
Hemoglobin	12 g/dl	12–16 g/dl
White blood cells	$5.4 \times 10^9/L$	$4.5\text{--}11.0 \times 10^9/L$
Platelets	$567 \times 10^9/L$	$150\text{--}450 \times 10^9/L$
Clinical chemistry		
Alanine aminotransferase (ALT)	3,716 Unit/L	0–35 Unit/L
Albumin	31 g/L	31–43 g/L
Alkaline phosphatase	223 Unit/L	36–92 Unit/L
Aspartate aminotransferase (AST)	3972 Unit/L	0–35 Unit/L
Bilirubin (total)	10 mg/dL	0.3–1.2 mg/dL
Blood urea nitrogen (BUN)	1.8 mmol/L	2.9–7.1 mmol/L
Creatinine	54 μ mol/L	61.9–115 μ mol/L
Glucose	5.5 mmol/L	3.9–5.8 mmol/L
Potassium	3 mmol/L	3.5–5 mmol/L
Prothrombin time (PT)	49.8 sec	11–13 sec
International normalized ratio (INR)	3.6	0.8–1.2
Sodium	130 mmol/L	136–145 mmol/L

3 | DISCUSSION

This 48-year-old woman, known to have inactive chronic hepatitis B virus (HBV), developed acute liver failure (ALF) induced by HBV reactivation (HBVr) 3 weeks after receiving the fourth cycle of doxorubicin and cyclophosphamide chemotherapy for adjuvant treatment of breast cancer, even though she had been on entecavir prophylaxis. Doxorubicin, a cytotoxic antineoplastic antibiotic, and cyclophosphamide, an alkylating agent, remain important agents in many cancer chemotherapeutic regimens. Current indications include leukemias, lymphomas, and breast cancer. Serum aminotransferase elevations occur in 40% and 43% of patients on doxorubicin and cyclophosphamide therapies, respectively. However, elevations are generally asymptomatic and transient, resolving even with the continuation of therapy.^{5,6} Doxorubicin and cyclophosphamide have been rarely implicated with severe and fatal acute liver injury and jaundice. Moreover, these two agents on their own have not been specifically linked to any case of ALF.⁶

A competing cause of ALF is HBVr which may occur in patients with chronic or resolved HBV infection receiving immunosuppressive therapy for cancer, autoimmune disease, or organ transplantation.⁷ Major practice guidelines recommend routine screening for chronic HBV in all patients undergoing cytotoxic and immunosuppressive chemotherapy.⁸ The technical review on prevention and treatment of HBVr during immunosuppressive drug therapy published by the American Gastroenterological Association in 2015 has considered doxorubicin a high-risk drug causing HBVr in 15%–30% of HBsAg-positive patients.⁹ The studies have also shown that HBVr occurs in approximately 20% of HBsAg-positive women receiving adjuvant chemotherapy with doxorubicin and cyclophosphamide for breast cancer^{10–12} (reviewed in Perrillo et al. 2015).⁹ In those studies, however, only one death due to HBVr-associated ALF was reported in the entire group of 154 patients.⁹ For HBVr risk, prophylactic treatment with entecavir or tenofovir (or lamivudine, if these drugs are not feasible therapeutic options) is routinely recommended at the initiation of chemotherapy.^{9,13,14} A recent meta-analysis suggested that entecavir prophylaxis in patients with chronic or resolved HBV infection undergoing chemotherapy is more effective than lamivudine for preventing HBVr.¹⁵

In this case report, we confirmed the diagnosis of ALF with signs of liver damage (elevated serum transaminases), impaired liver function (jaundice, prolonged prothrombin time, and INR >1.5), and severe (Grades 3–4) hepatic encephalopathy with cerebral edema. Viral etiology with HBVr was confirmed based on the patient's history of chronic HBV and the high level of HBV DNA (50,000 IU/ml). The HBVr was induced by her adjuvant doxorubicin and cyclophosphamide chemotherapy, even

though she had been on entecavir prophylaxis, probably because she was non-adherent to the medication. A recent study has reported a 70-year-old woman who experienced HBVr even with continuous entecavir prophylaxis and died of septic shock 4 months after CAR T-cell infusion for B-cell lymphoma.¹⁶ Hence, HBV DNA should still be closely monitored in patients undergoing immunosuppressive or cytotoxic therapy, even if entecavir prophylaxis is given.

In our patient, the high-grade encephalopathy with cerebral edema indicated critical and irreversible liver damage. Using King's College Criteria for prognostic assessment,² this patient had poor prognosis indicators including unfavorable etiology, age >40 years, and INR >3.5. Model for End-stage Liver Disease (MELD) Score (>30.5) also predicted the need for liver transplant.³ Regrettably, ALF induced by HBVr has been reported to be associated with a $\leq 20\%$ survival rate without liver transplant.^{1,17} Because of its rarity, ALF has not been studied in large, randomized trials, and most treatment recommendations represent expert opinions.¹ Emergent liver transplant is still the only effective intervention in patients with poor prognostic assessment; however, it is not always possible. Endotracheal intubation may be required with high-grade encephalopathy to control oxygenation and ventilation.

Supportive treatment with rapid and effective intravenous volume resuscitation, metabolic stabilization with correction of hypoglycemia and acidosis, etiology-specific therapy, and early referral to a specialist liver transplant center are key interventions in the early stage of the syndrome.^{2,3} Cerebral edema and hepatic encephalopathy always require intensive management to prevent post-recovery neurologic complications.¹⁸ The European Association for Study of the Liver considers intravenous N-acetylcysteine (NAC) a standard of care at admission for all patients with ALF.² This suggestion is largely based on findings from several studies in which NAC was found to improve mortality and liver transplantation rate in patients with non-acetaminophen ALF.¹⁹ In contrast, the American Gastroenterological Association suggests using NAC in non-acetaminophen ALF only in the context of clinical trials.³

4 | CONCLUSIONS

Acute liver failure due to HBV reactivation in HBsAg-positive patients undergoing chemotherapy is tragically fatal. Therefore, compliance with prophylactic antiviral treatment and close monitoring of HBV DNA is still crucial during the therapy. Upon recognition, prompt initiation of etiology-specific therapy, intensive care protocols, and an urgent liver transplant are essential interventions. Although very rare, physicians should be aware of

this condition as the diagnosis and management can be challenging.

AUTHOR CONTRIBUTIONS

The author has made substantial contributions to the conception and design of the work, and acquisition, analysis, and interpretation of data for the work; drafting the work and revising it critically for important intellectual content; final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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CONFLICT OF INTEREST

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

DATA AVAILABILITY STATEMENT

Data will be made available, if requested.

ETHICAL APPROVAL

This study is exempted from ethical approval from the Jazan Health Human Research Ethics Committee.

CONSENT

Written informed consent was obtained from the patient's guardian for the publication of this case report.

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