Hepatitis B Virus Reactivation Superimposed Hepatitis A Co-Infection Leading to Acute on Chronic Liver Failure: A Case Report and Literature Review

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ABSTRACT

Acute-on-chronic liver failure (ACLF) is a severe condition with an incidence rate of 5.7 cases per 1,000 person-years. A primary trigger for ACLF is hepatitis B reactivation, which is responsible for 40-60% of cases. Co-infection with hepatitis A can also contribute to its occurrence.

This study presents the case of a 58-year-old male patient with a history of hepatitis B virus (HBV)-related cirrhosis, presenting with symptoms including confusion, disorientation, worsening jaundice, abdominal discomfort, nausea, vomiting, loss of appetite, malaise, muscle pain, and fever. Despite regular treatment for HBV, the patient's condition deteriorated over 14 days. He had no history of hypertension, diabetes, autoimmune diseases, alcohol consumption, or smoking. On examination, the patient exhibited grade 2 hepatic encephalopathy, severe jaundice, ascites, and lower limb edema. Laboratory results revealed elevated liver enzymes, increased bilirubin levels, and decreased albumin. Subsequent testing confirmed acute hepatitis A infection and a significant hepatitis B viral load.

The report highlights that reactivation of Chronic Hepatitis B, accompanied by co-infection with hepatitis A, played a critical role in inducing inflammation and worsening the ACLF condition.

Keywords: *Acute-on-Chronic Liver Failure, Hepatitis B, Reactivation, Co-infection Hepatitis A.*

INTRODUCTION

Acute-on-chronic liver failure (ACLF) is a life-threatening clinical syndrome that causes a sudden worsening of liver function, characterized by severe systemic inflammation and a high risk of short-term death.[1–3] The precipitating events can be categorized as hepatic or non-hepatic. Among the most common causes are reactivation of chronic hepatitis B virus (HBV) infection, acute hepatitis A and E virus (HAV/HEV) infections, alcohol-associated hepatitis (AH), and acute bacterial infections.[2] Alcohol-related cirrhosis is the primary cause of chronic liver disease in Western countries, with bacterial infections being the leading trigger for ACLF. Conversely, HBV infection is the most prevalent cause of liver disease in the Asia-Pacific region, and HBV reactivation is the most common trigger for ACLF.[3,4]

HBV reactivation, characterized by the sudden reappearance or increase of HBV DNA in the serum of a patient with previously inactive or resolved HBV infection, is regarded as the primary cause of acute hepatic insult in chronic hepatitis B (CHB) patients in East Asia. This reactivation is mainly due to an imbalance between the host immunity and viral replication.[5] Hepatitis A virus (HAV) is one of the most common global causes of acute viral hepatitis. HAV is transmitted via the fecal-oral

route. Although the symptoms are typically self-limiting, HAV can occasionally result in liver failure and death.[6] Only a few cases report the occurrence of ACLF caused by HBV with superimposed hepatitis A infection. A superinfection of HAV in individuals with HBV can occasionally result in critical conditions in HBV carriers, irrespective of whether cirrhosis is present. Nevertheless, those with advanced fibrosis or cirrhosis are more susceptible to severe complications.[7]

This study presents a case report of a male previously diagnosed with chronic hepatitis B who is now experiencing reactivation alongside a hepatitis A infection, resulting in multi-organ damage that has induced ACLF.

CASE ILLUSTRATION

A 58-year-old male was admitted to our hospital after suffering an altered mental status and disorientation in time and space one day before admission. The patient had also experienced jaundice for the past 14 days, which had been progressively worsening. Additionally, the patient reported abdominal discomfort, nausea, vomiting, anorexia, malaise, myalgia, and fever. He had a history of HBV-related cirrhosis and had been receiving regular therapy. There was no history of hypertension, diabetes, or autoimmune disease, and none of his family members had similar complaints. The patient's wife stated that her husband is not an alcoholic and is a non-smoker. On physical examination, the patient's Glasgow Coma Scale (GCS) score was 12-13. He displayed Grade 2 hepatic encephalopathy and was noticeably disoriented and confused. His vital signs were within normal limits, and he was found to have severe jaundice, with yellow discoloration of his sclera and skin. His abdomen showed positive signs of ascites, and there was pitting edema in his lower extremities.

The results of the laboratory tests showed bicytopenia in the complete blood count, with a leukocyte count of 2.52 thousand/mm³ (normal range: 4-10 thousand/mm³) and a platelet count of 44 thousand/mm³ (normal range: 150-450 thousand/mm³). The liver function test results were elevated, including an aspartate transaminase (AST) level of 868 U/L (normal range: <40 U/L), an alanine transaminase (ALT) level of 443 U/L (normal range: <41 U/L), a total bilirubin level of 11.13 mg/dL (normal range: <4.1 mg/dL), a direct bilirubin level of 6.78 mg/dL (normal range: <0.2 mg/dL), and an albumin level of 2.7 g/dL. The serologic test for IgM anti-HAV yielded a positive result with a value of 0.030 (reactive ≤1.0), and the HBV DNA was measured at 1.14 x 10^7 IU/mL log 7.06.

The patient was admitted to the hospital with a diagnosis of] ACLF resulting from hepatitis B reactivation and concurrent hepatitis A infection. Upon arrival, the patient was transferred to the intensive care unit (ICU) and began receiving supportive therapy. This included intravenous fluids to maintain hydration, antibiotics,

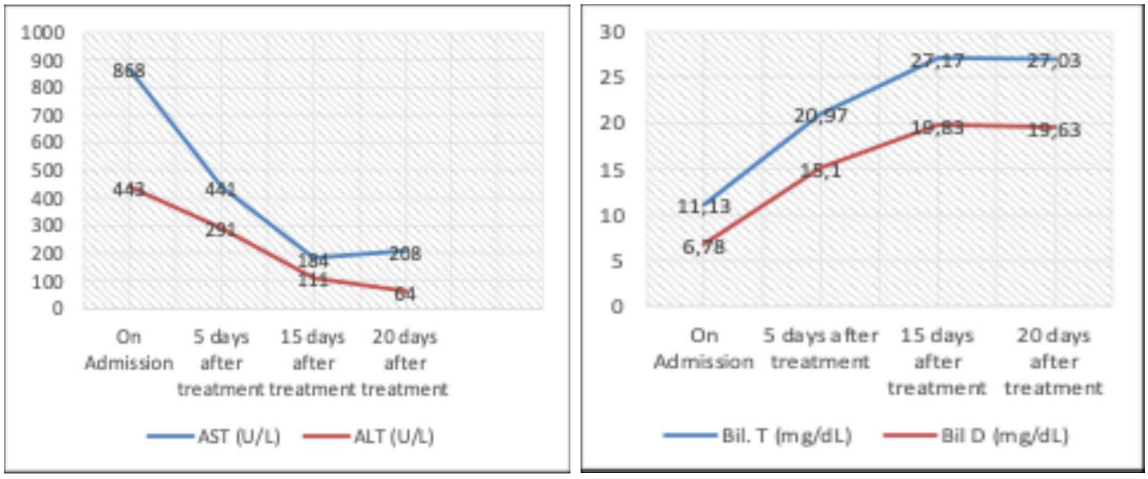

Figure 1. Data on laboratory result changes

nucleos(t)ide analogues (NAs), non-selective beta-blockers (NSBBs), hepatoprotectors, albumin infusion, and lactulose. The patient's condition was monitored, and further serial diagnostic tests were conducted (**Figure 1**). Regrettably, despite all efforts, there were no signs of improvement, and the patient's condition continued to deteriorate, ultimately resulting in his demise after approximately one month of treatment.

DISCUSSION

In the past decade, different international consortia have developed various definitions of ACLF. The Asian Pacific Association for the Study of Liver (APASL) defines ACLF as an acute hepatic insult manifesting as jaundice (serum bilirubin ≥ 5 mg/dL) and coagulopathy (INR ≥ 1.5 or prothrombin activity < 40%), which is further complicated within four weeks by the development of ascites and/or encephalopathy in a patient with either previously diagnosed or undiagnosed chronic liver disease. Conversely, the definition provided by the European Association for the Study of the Liver–Chronic Liver Failure (EASL-CLIF) Consortium and the North American Consortium for the Study of End-Stage Liver Disease includes the additional criteria of extrahepatic organ failures and the significance of extrahepatic precipitating events.[1,3,4,8–10] The APASL ACLF incidence rate was 5.7 cases per 1,000 person-years (95% CI: 5.4 – 6.0), while the EASL ACLF had an incidence rate of 20.1 (95% CI: 19.5 – 20.6).[11]

HBV-related ACLF has been previously defined according to the general definitions of ACLF. Therefore, it remains uncertain whether these definitions are adequately suited for pure HBV-ACLF.[12] The Chinese Group on the Study of Severe Hepatitis B-ACLF (COSSH-ACLF) has defined HBV-ACLF as a complex syndrome with high short-term mortality that occurs in patients with HBV-related chronic liver disease, regardless of the presence of cirrhosis. This syndrome is characterized by an acute deterioration of liver function accompanied by hepatic and/or extrahepatic organ failure. The COSSH-ACLF group proposes that patients with chronic hepatitis B, with or without cirrhosis, should be diagnosed with ACLF if they exhibit a total bilirubin level of ≥ 12 mg/dL and an INR of ≥ 1.5. This definition could identify 20% more patients, thereby enhancing their chances of receiving timely and appropriate treatment. The group has found these criteria to be significantly more sensitive than the EASL-ACLF criteria for diagnosing patients with HBV-ACLF.[12,13]

The precipitating events in HBV-related ACLF can be categorized into intra-hepatic or hepatic and extra-hepatic or systemic insults. While spontaneous reactivations of hepatitis B are the most common hepatic precipitating factor, accounting for approximately 40-60% of cases, other significant causes include superinfection with other hepatotropic agents, superimposed drug-induced liver injury (DILI), superimposed alcoholic hepatitis, and insults such as bacterial infections and gastrointestinal bleeding with shock. Among extra-hepatic or systemic causes, bacterial infections account for 20-30% of HBV-related ACLF cases. The diagnostic criteria for these common precipitants, including reactivations of HBV infection and superimposed with HAV infection, are outlined in **Table 1**.[2,12,14,15]

According to the American Association for the Study of Liver Disease (AASLD), reactivation of chronic hepatitis B is a well-defined syndrome characterized by the sudden reappearance or rise of HBV DNA in the serum of a patient with a previously inactive or resolved HBV infection, where there was no prior virological, biochemical, or histological evidence of active virus infection or disease.[16,17] HBV reactivation is assessed according to the 2018 recommendation of AASLD as an increase in HBV DNA levels by ≥ 2 log IU/mL from baseline or the reappearance of HBV DNA viremia or HBsAg in individuals who previously had detectable HBV DNA or HBsAg. This reactivation can occur due to the withdrawal of antiviral drugs, resistance to nucleotide analogues, or following treatment with immunosuppressive and chemotherapeutic drugs.[5,18,19]

According to a study, the predominant cause of HBV reactivation was the withdrawal or interruption of antiviral drugs. Among the 529

patients who experienced HBV reactivation, 70.9% of reactivations were triggered by the cessation of antiviral treatment. Despite detailed recommendations on nucleos(t)ide analogues (NAs) treatment and withdrawal provided by APASL, EASL, and AASLD guidelines, poor adherence to NAs treatment remains common in clinical practice. Reported treatment adherence rates range from 46.4% to 74.6%, leading to virological breakthroughs and increased mortality.

Therefore, it is crucial to focus on improving adherence to antiviral treatment in chronic hepatitis B patients to prevent HBV reactivation and its associated severe outcomes.[5]

Dual infection, also known as co-infection, is a phenomenon that has been documented in numerous developing and developed countries. Reports from developing countries have noted HBV/HAV co-infections, which can serve as precipitating events in ACLF. A total of 310,746 cases of acute hepatitis A were observed during the Shanghai hepatitis A epidemic, with 47 fatalities (0.015%). The fatality rates were 0.05% (15 out of 27,346) for patients with HBV infection and 0.009% (25 out of 283,400) for those without HBV infection. Notably, the fatality rate was 5.6 times higher in patients with HBV infection than in those without.[7]

Inflammation, both hepatic and systemic, is the primary driver of HBV-associated ACLF. It involves a complex interplay of host fitness impairment, tolerance mechanisms, defense strategies, and dysregulated inflammatory responses. Functionality is significantly altered compared to healthy individuals. HBV proteins, such as the hepatitis B antigen, impair the

Table 1. Potential precipitants of ACLF[15]

Precipitants	Diagnosis
Spontaneous bacterial peritonitis	**Neutrophils in ascites ≥ 250/mm**
Spontaneous/secondary bacteremia	Spontaneous bacteremia: positive blood cultures and no cause of bacteremia; secondary bacteremia: (1) catheter-related infection (positive blood and catheter tip cultures); (2) bacteremia occurring within 24 hours after an invasive procedure
Urinary tract infection	Abnormal urinary sediment (>10 leukocytes/ field) and positive urinary culture, or an excessive number of leukocytes per field if cultures are negative
Alcohol-related hepatitis	Active alcohol consumption and, if a liver biopsy is not available, use the NIAA criteria, which include the presence of at least three of the following: (1) Serum bilirubin > 3 mg/dL (>50 µmol/L), (2) AST > 50 IU/mL, (3) AST/ALT ratio > 1.5, (4) AST and ALT < 400 IU/mL Macro vesicular steatosis must be present for a liver biopsy, along with at least one of the following: neutrophil infiltration, hepatocyte injury (ballooning), or Mallory-Denk bodies. Additionally, the presence of megamitochondria, satellitosis (neutrophils surrounding dying or dead hepatocytes), and cholestasis (bilirubin stasis) is common and may be related to prognosis.
Gastrointestinal hemorrhage with shock	Hematemesis, melena, low hemoglobin levels, a sudden decrease in hemoglobin levels (≥2 g/dL), or any combination of these conditions, along with hypovolemic shock; endoscopy is recommended.
Epstein-Barr virus (EBV)	AST and ALT levels exceeding three times the upper limit of normal (ULN) IU/mL, along with detection of viral capsid antigen (VCA)-IgM antibody, early antigen (EA-D) antibody, Epstein-Barr nuclear antigen (EBNA) antibody, and EBV quantitative PCR.
Cytomegalovirus (CMV)	AST and ALT levels exceeding three times the upper limit of normal (ULN) IU/mL, along with CMV IgG antibody detection and CMV quantitative PCR.
Hepatitis B virus (HBV) infection or reactivation	Elevated AST and ALT levels, increased HBV DNA, elevated HBsAg (which may be negative in S-variants), and 10-25% positivity for anti-HBc IgM.
Superimposed hepatitis D in patients with chronic HBV	AST and ALT > 400 IU/ml, positive HDV IgM and IgG, elevated PCR (HDV RNA)
Superimposed hepatitis A	AST or ALT levels greater than 400 IU/mL, serum bilirubin exceeding 3 mg/dL (> 50 µmol/L), and positive anti-HAV-IgM.
Superimposed hepatitis C	AST or ALT > 400 IU/ml, serum bilirubin > 3 mg/dl (> 50 µmol/L) and elevated HCV RNA
Drug-induced liver injury	Medications or herbal supplements that cause liver damage.

ability of Kupffer cells to express Toll-like receptors, inhibit the proliferation of specific T lymphocytes, and reduce the secretion of interferon-γ and IL-10. Studies involving HBV-ACLF patients indicate that while the number of myeloid and plasmacytoid dendritic cells remains stable during chronic HBV infections, their numerous mutations in HBV surface antigen-encoding genes associated with HBV-immune escape have been identified in HBV-ACLF patients. Additionally, ACLF patients exhibit higher counts of circulating neutrophils and monocytes but have lower lymphocyte counts compared to non-ACLF patients. Neutrophils in patients with decompensated cirrhosis and ACLF show impaired phagocytosis, reactive oxygen species production, and bactericidal activity but an increased capacity to form neutrophil extracellular traps. The monocyte-macrophage system in ACLF patients is significantly inhibited, with reduced secretion of proinflammatory factors, diminished bacterial killing, oxidative burst, and phagocytosis. Studies have also demonstrated that HBV reactivation can result in a substantial increase in HBV-specific CD4+ and CD8+ T lymphocytes, leading to liver damage.[3,12]

ACLF patients often have underlying chronic liver disease; therefore, they require comprehensive care, including the diagnosis and treatment of precipitating events and supportive therapy. Due to their rapid deterioration and high short-term mortality rates, careful assessment, vigilant monitoring, and intensive care unit (ICU) management by liver specialists are crucial. For those with life-threatening single or multiple organ failure who do not respond to standard treatments, organ support in the ICU, along with continuous and dynamic monitoring, is essential. Additionally, access to a liver transplant unit and facilities for organ support and bridging therapies should be readily available.[2,20]

The early and rapid reduction of HBV DNA levels can help suppress hepatocellular necrosis and cytokine release, potentially slowing or reversing the progression of the disease.[3] Nucleos(t)ide analogues (NAs) treatment should be promptly administered to all patients presenting with a hepatitis B virus infection, pending confirmation through viral DNA levels. Potent antiviral agents, including tenofovir, tenofovir alafenamide, and entecavir, should be utilized.[20]

In a recent study, approximately 37% of patients with ACLF were found to have a bacterial infection at the time of diagnosis. Additionally, 46% of the remaining ACLF patients developed bacterial infections within the subsequent four weeks. Multidrug-resistant (MDR) pathogens were implicated in one-third of these cases, with regional variations in prevalence. Consequently, a systematic search for infection, including microbiological and cytological analyses of ascitic fluid, should be routinely conducted upon admission. Empirical antibiotic therapy should be promptly initiated, tailored to the suspected infection site with local microbial ecology. Broad-spectrum antibiotics are recommended for severe infections or when risk factors for MDR pathogens are present.[8]

Fluid therapy should primarily use crystalloids, while balanced salt solutions can help minimize the risk of hyperchloremic acidosis and subsequent kidney complications. However, the beneficial effects of albumin resuscitation in patients with cirrhosis extend beyond simple volume expansion. Albumin levels decrease overall, and its function is impaired due to alterations in its chemical structure, leading to a reduced binding capacity for bacterial products, reactive oxygen species, and other mediators involved in ACLF. Some studies indicate that albumin may help modulate systemic oxidative stress and inflammation or restore immune defense.[21]

Hepatic encephalopathy (HE) occurs in up to 40% of cases and is associated with high mortality. Arterial ammonia levels exceeding 140 mcg/dL, particularly in grades III–IV HE, are linked to elevated mortality rates. Ammonia-lowering therapies, such as lactulose and rifaximin, have demonstrated significant improvements in HE scores. Mechanical ventilation may be necessary in cases of advanced HE.[2]

Acute variceal hemorrhage (AVH), which constitutes approximately 70% of all upper gastrointestinal bleeding episodes in cirrhosis, is a significant cause of mortality in these patients, with a six-week mortality rate of

about 20%. Recent advancements in the management of AVH, including endoscopic interventions and pharmacological treatments with the combination of a safe vasoconstrictor (terlipressin, somatostatin, or analogues such as octreotide or vapreotide), and the use of transjugular intrahepatic portosystemic shunt (TIPS), have contributed to a reduction in the frequency of variceal bleeding over the past decade.[15,20]

Nonspecific beta-blockers (NSBBs) were initially used over 40 years ago to prevent variceal bleeding, but their use has expanded to prevent recurrence and manage cirrhosis complications. However, their effectiveness in patients with ascites or spontaneous bacterial peritonitis (SBP) is debated, as some studies indicate a higher risk of death associated with NSBB use. NSBBs can be problematic in patients with ACLF due to hemodynamic instability and renal dysfunction, leading to dose reduction or discontinuation. The CANONIC study and a separate study of acutely decompensated cirrhosis patients showed mixed results. While NSBBs were associated with lower 28-day mortality rates and improved survival, concerns were raised about their safety in acute settings. These findings suggest a need for further research on the safety and efficacy of NSBBs in ACLF patients, particularly regarding the timing of reintroducing these drugs after recovery.[15]

Liver transplantation (LT) remains the definitive treatment for HBV-related ACLF when medical management fails to stabilize the patient. Studies indicate that 90-day survival rates can reach 90% and one-year survival can be 81% in LT, even with multiple organ failures. [2,12]

Several scoring systems can be used to predict ACLF patients' outcomes, including CLIF-C ACLF, Child-Pugh, MELD, and MELD-Sodium. Although the MELD score has shown an advantage in displaying a short-term prognosis for ACLF patients in a study, the CLIF-C ACLF score is more highly recommended for patients who have developed complications such as encephalopathy, bleeding, or ascites.[22,23]

ACLF remains a significant challenge in hepatology. It is known that the prognosis of ACLF is very poor due to cerebral encephalopathy. ACLF may have a good prognosis if patients have access to emergency liver transplantation (ELT). Therefore, access to a liver transplant unit and facilities for organ support and bridging therapies should be readily available.[24]

CONCLUSION

Severe inflammation caused by reactivation of Chronic Hepatitis B co-infection with Hepatitis A worsened the clinical course of ACLF. Managing ACLF could be a clinical challenge, yet without liver transplantation, the prognosis is known to be very poor.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICS STATEMENT

Informed consent was obtained from the patient and family to publish this case report.

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