

Comprehensive treatment of acute-on-chronic liver failure in a patient with hepatitis B: a case report

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Abstract The clinical data of a patient with acute-on-chronic liver failure were analyzed retrospectively. The patient has suffered from hepatitis B for 30 years. His liver function deteriorated, yielding Child-Pugh grade C and reaching a model for end-stage liver disease score of 33 points within a short period; this condition was complicated with highly active variceal bleeding and coagulation system failure (PT > 100 s). The patient also presented hepatocellular carcinoma. Comprehensive treatments included effective inhibition of hepatitis B virus replication and intensive care support. Piggyback orthotopic liver transplantation was performed as the final treatment. The patient recovered uneventfully and was discharged after surgery.

Keywords acute-on-chronic liver failure; submassive necrosis; viral hepatitis B; esophageal variceal bleeding; liver transplantation

Introduction

Acute-on-chronic liver failure (ACLF), a common acute critical illness in clinical settings, is difficult to treat and accounted for high short-term mortality [1,2]. Furthermore, the mortality rate of ACLF in three months is >50%. Liver transplantation is an effective option to treat ACLF. The onset of acute liver failure in patients with chronic liver disease is often complicated by the failure of vital organs manifested in various adverse reactions, such as coagulation system failure, esophageal variceal bleeding, and/or sepsis, including spontaneous bacteria peritonitis; these conditions may result in high morbidity and mortality before and after transplant surgery. The preoperative care experiences of this patient were reviewed in this case report. Such experiences are relevant to the treatment of ACLF and pose challenges to the clinical medical skills of physicians.

Case presentation

The patient was a 55-year-old man admitted with chief

complaints of jaundice and abdominal distension for two weeks. This patient also manifested symptoms of a suspicious liver mass that was detected one week earlier. He also suffered from jaundice and abdominal distension without evident reason two weeks ago; however, he did not consider these symptoms as serious and did not seek further treatment. He visited a hospital as the symptoms worsened and vomited once during the visit. He did not experience fever, headache, dizziness, diarrhea, or other discomfort. His liver function parameters were listed as follows: ALB 27 g/L; TB 377.9 μmol/L; CB 309.5 μmol/L; ALP 218 U/L; ALT 159 U/L; AST 155 U/L; and AFP 213 ng/ml. Renal function and electrolytes were normal. The following hepatitis B virus (HBV) markers were also detected: HBsAg (+); HBeAg (-); HBeAb (+); HBcAb (+); HBV-DNA > 5 × 10⁷ copies/ml; ANA (-); and AMA (-). Abdominal ultrasound results showed gallstones with gallbladder wall edema, ascites, and cirrhosis of the liver. Abdominal CT results showed cirrhosis with portal hypertension, a visible nodule measuring 2 cm in the right lobe, intrahepatic bile duct dilatation, and portal vein and splenic vein thrombosis. Spironolactone was administered; ascites puncture and biochemical and bacteriological tests were performed, but the results showed no abnormalities. After 3 d, renal dysfunction was identified and showed the following parameters: BUN 11.4 mmol/L; Scr 132.75 μmol/L. Diuretic treatment was then discontinued. Gastro-

scopy results showed severe esophageal varices without history of ligation. Nadolol was administered to reduce portal pressure. The patient poorly responded to treatment; as such, he was transferred to our hospital for further treatment. He has suffered from hepatitis B for 30 years and revealed a history of repeated liver function abnormalities. However, no jaundice was observed two weeks ago. He did not undergo anti-HBV therapy. His personal history showed that he does not smoke or consume alcoholic beverages.

The following physical examination results were documented upon admission: temperature, 37.2 °C; blood pressure, 120/80 mmHg; R, 18 beats/min; and heart rate, 85 beats/min. The patient was conscious and manifested symptoms of chronic liver disease. Jaundice of the skin and sclera was present. Liver palms and spider angioma were detected, and superficial lymph nodes were not detected. The heart and the lung remain normal, but abdominal distension was visible. Abdominal wall veins could also be observed. Neither varicose nor abdominal tenderness was detected. The liver was not palpable. The spleen was detected two fingers below the ribs. Shifting dullness was positive. Ankle edema was present in both lower extremities. Nervous system test showed negative results.

The following blood routine test results were obtained after admission: WBC 2.31×10^9 /L; RBC 3.13×10^{12} /L; HGB 104 g/L; and PLT 49×10^9 /L. The following liver function parameters were also recorded: ALB 31 g/L; TB 348.5 μ mol/L; ALP 218 U/L; ALT 107 U/L; AST 125 U/L; Scr 125 μ mol/L; PT 20.3 s; and INR 1.76.

Diagnosis and treatment

Upon admission, the patient exhibited Child-Pugh C liver function with a model for end-stage liver disease (MELD) score of 27. Considering that HBV replication highly occurred, physicians prescribed entecavir as anti-HBV therapy combined with supportive liver protection, coagulation factor and albumin replacement, and other supportive treatments. However, his liver function and blood coagulation indicators continued to deteriorate and his MELD score increased to 33. One week after admission, hematemesis (dark blood with clots) reaching 1500 ml was observed without evident cause. A transient decrease in blood pressure to 87/45 mmHg was also noted. At this time, liver function parameters were recorded as follows: TB/CB, 429.4/298.0 μ mol/L, ALB 27 g/L, ALT 83 U/L, AST 110 U/L, ALP 74 U/L, and γ -GT 48 U/L. The following renal function parameters were also documented: BUN 6.9 mmol/L; Scr 147 μ mol/L; PT 26.9 s; INR 2.32; and fibrinogen 57 mg/dl. Blood routine test results revealed the following: WBC 2.64×10^9 /L; RBC 1.92×10^{12} /L; Hb 67 g/L; and BPC 41×10^9 /L. Venous access was immediately established for fluids and blood transfusions to maintain the subject's vital

signs. Lyophilized fibrinogen, human prothrombin complex, and other replacements were also administered to improve coagulation. Somatostatin (250 μ g/h) was infused intravenously but failed after 12 h. The combined therapy of somatostatin and intravenous terlipressin (1 mg/q8h) was then administered. Intravenous broad-spectrum antibiotics were also administered to manage endotoxemia and reduce portal pressure. As hemorrhage gradually ceased, his stool turned yellow in 3 d. However, a repeat coagulation showed PT > 100 s and fibrinogen < 40 mg/dl, suggesting liver failure and a serious inhibition of clotting factor synthesis. As coagulation deteriorated sharply, cryoprecipitate, coagulation factors, frozen plasma, and fibrinogen infusion were immediately administered. After 3 d, a repeat coagulation showed PT 18.6 s and fibrinogen 153 mg/dl; this result indicated a significant improvement in terms of the previous parameters. The following liver function parameters were obtained: TB/CB 379.4/314.1 μ mol/L, ALB 32 g/L, ALT 143 U/L, AST 185 U/L, ALP 94 U/L, and γ -GT 48 U/L. The following renal functions were also detected: BUN 4.9 mmol/L and Scr 88 μ mol/L. These results indicated that the patient was in a stable condition; as such, he was transferred to the surgical ward for orthotopic liver transplantation. During surgery, severe cirrhosis and sclerosing nodules measuring 0.5 cm to 0.8 cm were observed. Portal vein emboli were detected along the portal vein, and varicose veins of the portal branches were evident. A mass with dimensions of approximately 2.5 cm \times 2.0 cm \times 2.0 cm was detected in the liver, particularly in the right lobe VIII section, with clear boundaries and no envelope (Fig. 1). After a successful surgery was performed, the patient safely returned to the ward. Examination of the resected specimen revealed pathological findings of grade III hepatocellular carcinoma with necrosis (Fig. 2). Volume replacement, anti HBV virus, anti-infective, and anti-rejection therapy were administered actively after surgery. The patient was maintained in a stable condition and the liver function was gradually recovered. The liver function test 19 days after surgery showed the following: TB/CB 23.8/20.2 μ mol/L; ALB 50 g/L; ALT 47 U/L; AST 28 U/L; ALP 149 U/L; and γ -GT 57 U/L. The following renal function parameters were obtained: BUN 12 mmol/L and Scr 72 μ mol/L. Blood routine test results were listed as follows: WBC 2.82×10^9 /L; RBC 3.18×10^{12} /L; Hb 98 g/L; BPC 214×10^9 /L; and PT 11.7 s. The following HBV markers were also detected: HBsAg (-); HBsAb(+); HBeAg(-); HBeAb (+); HB_cAb (+); and 2.1 ng/ml AFP. He was discharged 22 days after surgery. Follow-up tests showed normal liver function; liver ultrasound findings were also normal.

Discussion

The core clinical elements of ACLF, such as acute deterioration of hepatic functions, multiple organ failure,



Fig. 1 Macroscopic view of the specimen (total hepatectomy).

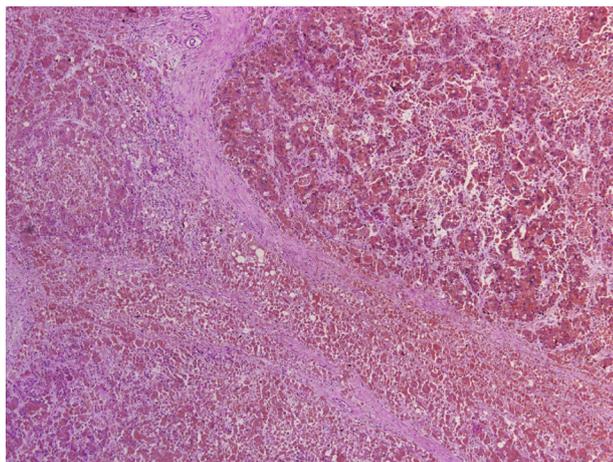


Fig. 2 Hepatocellular carcinoma with necrosis, differentiation grade III. HE staining 100 \times .

and deranged systemic inflammatory responses, have been commonly recognized [1]. The present patient with chronic liver disease caused by HBV experienced a short-term increase in bilirubin (total bilirubin $>171 \mu\text{mol/L}$), a prothrombin time international normalized ratio ≥ 1.5 , and a MELD score ≥ 16.1 points, complicated by organ failure (huge active GI bleeding and coagulation system failure with PT >100 s); this result is consistent with the diagnosed characteristics of ACLF [1,3]. The pathological findings showed nodular cirrhosis with significant inflammatory reaction and severe fibrosis, bile duct hyperplasia and cholestasis in the surrounding liver tissue (Fig.3). It mostly is the consequence of submassive necrosis of liver which is the solid evidence that the patient has undergone ACLF. A number of causes can contribute to liver failure. In Asia, HBV reactivation is considered as one of the most common acute

inducers leading to ACLF in patients with HBV-related cirrhosis or chronic hepatitis B [4]. The pathogenesis of hepatic failure in hepatitis B is associated with the continuous replication and expression of HBV and compromised host immune response. Therefore, the effective inhibition of HBV replication is a major factor in treatment. For patients suffering from HBV-related liver failure, active therapy should be administered in combination with quick, powerful therapy throughout the course based on the patient's medical history, virus mutation, and viral load [5]. Entecavir is an internationally recognized, potent, and selective guanosine analog. Entecavir is converted into an active triphosphate via phosphorylation in the human body and then competes with polymerase natural substrate deoxyguanosine triphosphate; as a result, the initiation of HBV replication, reverse transcription, and synthesis are inhibited and a strong antiviral effect is elicited [6]. With the extremely high load of HBV replication in the patient in this study, entecavir was immediately administered to inhibit viral replication and the liver function including prothrombin time was improved.

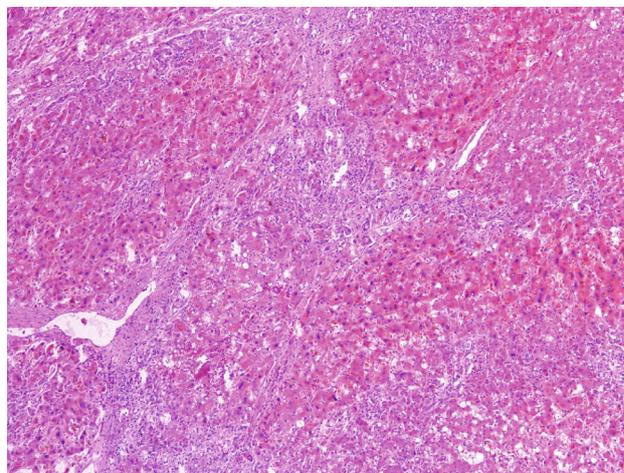


Fig. 3 Nodular cirrhosis with significant inflammatory reaction and severe fibrosis, bile duct hyperplasia and cholestasis. HE staining 50 \times .

Acute variceal hemorrhage is a fatal complication manifesting organ failure in the patient in this study. Studies have confirmed that somatostatin and its analog octreotide can reduce portal pressure without affecting systemic blood flow. However, somatostatin or its analogs do not yield the desired effect in some patients with acute variceal bleeding. Terlipressin is a vasopressin that can disrupt glycy residues catalyzed by endopeptidase after intravenous injection; lysine vasopressin is then released for a prolonged duration to reduce portal pressure. The combination of these two drugs

can elicit an even stronger hemostatic effect [7]. In this case study, the patient was initially treated with somatostatin, which alone failed to control the bleeding but demonstrated a strong hemostatic effect in combination with terlipressin. In our experience, this combination treatment could be commonly used in clinical practice.

ACLF is often associated with coagulation disorders. Hence, preoperative supplement of prothrombin complex, cryoprecipitate, fibrinogen, and fresh plasma can be used. Cryoprecipitate, apheresis platelets, and other clotting substances can also be added depending on bleeding wounds and test results. The currently used coagulation factor complexes also help improve coagulation.

The patient in this study showed two indications of liver transplantation: ACLF and small hepatocellular carcinoma (HCC). The timing of transplantation is crucial to provide patients with ACLF with “Window” opportunity [1]. Prognosis is relevant when liver transplantation is performed. After HBV virus replication and complications are controlled, the patient exhibited temporary improvement. This condition indicates a good time for liver transplantation. The second indication of HCC fits the Milan criteria for liver transplantation.

In short, ACLF management challenges our best skills as physicians. Considering the pathophysiological characteristics of ACLF, we should focus on the treatment of underlying disorders and coagulation disorders (anti-HBV therapy), prevention of bleeding and severe infection (sepsis, systemic inflammatory response syndrome), maintenance of hemodynamic stability, and prevention of heart, lung, kidney, and other vital organ-related complications [8]. Comprehensive medical treatment aids the recovery of a small part of patients and can also improve liver function grade as part of preoperative preparation for transplantation.

Compliance with ethics guidelines

Lei Li, Yimei Liu, Tiancheng Luo, Jian Zhou, Yingyong Hou, Xizhong Shen, and Jiyao Wang declare that they have no conflict of interest. Informed consent from the patient was obtained.

References

1. Jalan R, Gines P, Olson JC, Mookerjee RP, Moreau R, Garcia-Tsao G, Arroyo V, Kamath PS. Acute-on-chronic liver failure. *J Hepatol* 2012; 57(6): 1336–1348
2. Olson JC, Kamath PS. Acute-on-chronic liver failure: concept, natural history, and prognosis. *Curr Opin Crit Care* 2011; 17(2): 165–169
3. Liver Failure and Artificial Liver Group, Chinese Society of Infectious Diseases, Chinese Medical Association. Severe Liver Disease and Artificial Liver Study Group, Chinese Society of Hepatology. Guidelines on the management of liver failure. *J Clin Hepatol (Shi Yong Gan Zang Bing Za Zhi)* 2006; 9: 321–324 (in Chinese)
4. Garg H, Sarin SK, Kumar M, Garg V, Sharma BC, Kumar A. Tenofovir improves the outcome in patients with spontaneous reactivation of hepatitis B presenting as acute-on-chronic liver failure. *Hepatology* 2011; 53(3): 774–780
5. Wang J. Clinical utility of entecavir for chronic hepatitis B in Chinese patients. *Drug Des Devel Ther* 2013; 8: 13–24
6. Matthews SJ. Entecavir for the treatment of chronic hepatitis B virus infection. *Clin Ther* 2006; 28(2): 184–203
7. Guo LY, Wang GJ. Clinical observation of somatostatin combined with terlipressin for acute esophageal variceal bleeding in cirrhosis patients. *China Pharm (Zhongguo Yao Fang)* 2012; 32 (in Chinese)
8. Rengstorff DS, Osorio RW, Bonacini M. Recovery from severe hepatitis caused by mushroom poisoning without liver transplantation. *Clin Gastroenterol Hepatol* 2003; 1(5): 392–396