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CASE REPORT | LIVER

Exertional Heat Stroke-Induced Acute Liver Failure and Liver Transplantation

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ABSTRACT

Exertional heat stroke is a medical emergency characterized by excessive heat production and inadequate heat dissipation usually after heavy exertion in hot and humid climates and can be associated with multiorgan failure. Treatment is largely supportive, but liver transplantation (LT) may be necessary in select patients. Here, we report the case of a 44-year-old runner who was found unconscious after a 5-mile run and developed acute liver failure. He underwent successful LT 1 week later when he developed encephalopathy. This case report illustrates the importance of early LT referral in patients with exertional heat stroke-induced acute liver failure.

INTRODUCTION

Exertional heat stroke (EHS) is a rare but serious medical emergency usually seen in younger individuals after strenuous exercise and is among the leading causes of death in young athletes.[1] It is characterized by hyperthermia (>40°C), central nervous system (CNS) dysfunction, and often multiorgan failure.[2] Common complications include acute liver failure (ALF), acute renal failure, disseminated intravascular coagulation (DIC), and death.[3] Hepatocellular injury occurs commonly in EHS and is usually reversible and managed supportively. However, cases of EHS-induced ALF can be fatal. Currently, no clear guidelines exist regarding the timing of liver transplantation (LT) in this patient population because of low disease prevalence and low number of LTs performed. In addition, electrolyte and organ derangements in EHS, such as CNS changes and DIC, can complicate evaluation for LT. Early consideration of LT is vital in this patient population.

CASE REPORT

A 44-year-old marathon runner with no past medical history presented to a local hospital after being found unconscious after a 5-mile run in the summer. The initial vitals showed temperature 39.4°C, heart rate 130 bpm, and blood pressure 80/50 mm Hg. He was intubated, fluid resuscitated, started on vasopressors and broad spectrum antibiotics, and admitted to the intensive care unit where he underwent external cooling. The initial laboratory results were notable for platelet 130 K/cu mm, Cr 2.5 mg/dL, aspartate aminotransferase 332 U/L (AST), alanine aminotransferase (ALT) 87 U/L, alkaline phosphatase 75 U/L, total bilirubin 0.5 mg/dL, lactate 5.8 mmol/L, CK 16K U/L, international normalized ratio (INR) 2.1, and fibrinogen <25 mg/dL. The viral hepatitis panel, acetaminophen level, and computed tomography scan of the head were negative. Renal replacement therapy was started, and the patient developed DIC that persisted despite multiple transfusions. Given the persistent coagulopathy and liver injury, he was transferred to our hospital for the consideration of LT on day 4 from initial presentation. His aspartate aminotransferase/alanine

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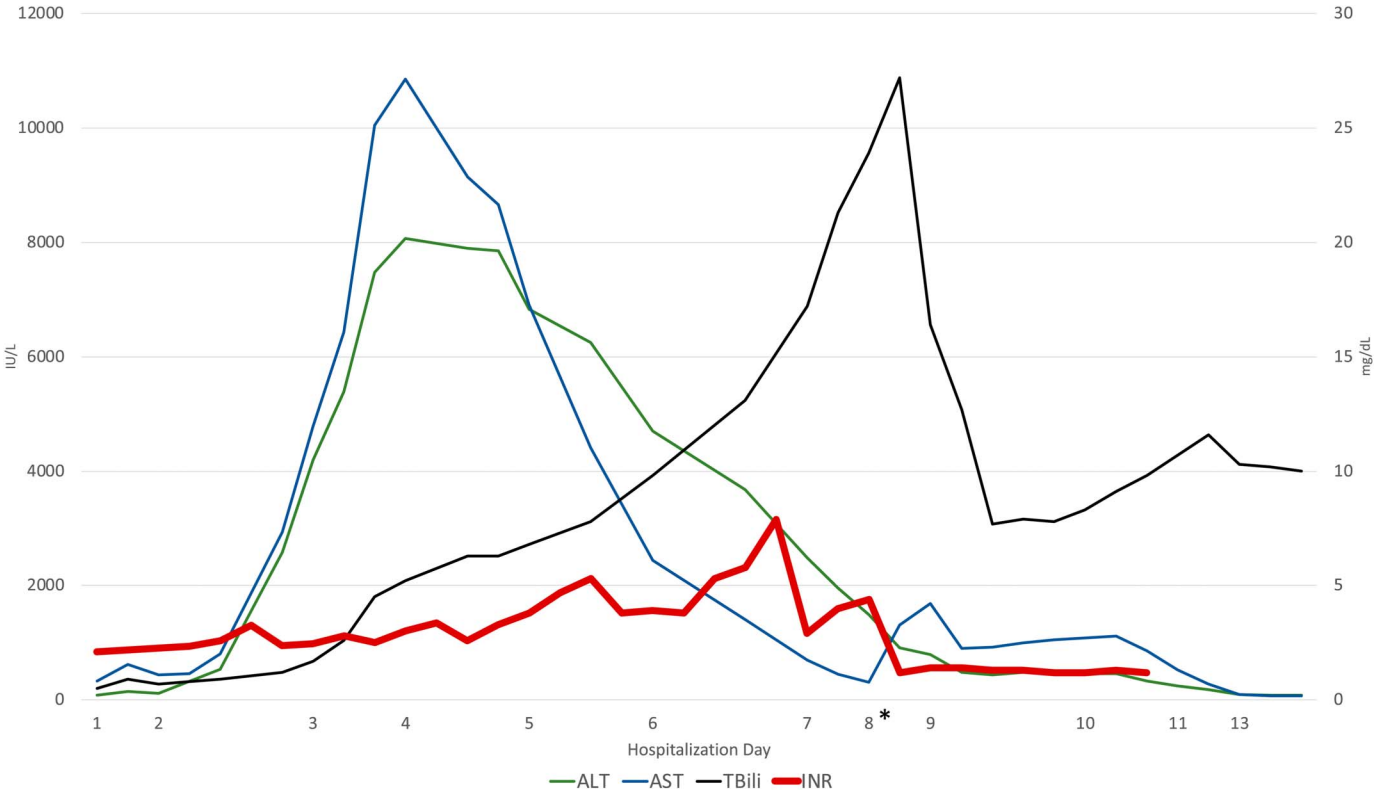

Figure 1. Trend of patient's alanine aminotransferase, aspartate aminotransferase, total bilirubin, and international normalized ratio during hospitalization. * Indicates day of liver transplantation. ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; TBili, total bilirubin.

aminotransferase had peaked, but his total bilirubin and INR continued to rise (Figure 1). Notably, his mental status was alert and interactive while intubated, and he was extubated successfully.

Intravenous N-acetylcysteine (NAC) was administered on days 5–8 from initial presentation. On day 5, he developed encephalopathy, manifesting as lethargy and disorientation. Ammonia level the day before was 81 μmol/L; computed tomography of the head was not performed. He was listed for transplant as status 1a for ALF on day 6 and underwent successful cadaveric LT on day 8. Liver explant pathology showed extensive hepatocyte necrosis (>80%) in zones 2 and 3 (Figure 2). The patient was discharged on day 33 with recovery of renal function and mental status. Three years after LT, he continues to do well with normal graft function.

DISCUSSION

Our case report demonstrates that EHS is a cause of ALF, and early consideration of LT may be lifesaving. As with any case of ALF, evaluation for LT must be initiated early and frequent clinical assessment is required with a particular focus on mental status to assess for the onset of encephalopathy. Although most cases of liver injury in EHS are asymptomatic and reversible, ALF has been documented in 5% of the patients with EHS.[4] Similar to ALF, EHS can also be characterized by CNS dysfunction and coagulopathy, which can make it difficult to discern whether the encephalopathy is from liver failure or EHS. The distinction is critical for the decision to list for LT. A multicenter study of patients with EHS/ALF found that poor prognostic factors included temperature >42°C, rapid multiorgan failure requiring artificial organ support, and the use of vasopressors.[5] In this study of 8 patients with EHS/ALF, only 1 underwent combined kidney/LT, 2 died within 48 hours of onset of multiorgan failure, and 5 recovered with supportive care. Similarly, another study found that 61.5% of the patients spontaneously recovered and 20% of the patients received LT.[6]

At the time of transfer, our patient did not meet the King's College Criteria for nonacetaminophen-related ALF. He met the criteria on day 6 (Grade II encephalopathy, INR >6.5), and ultimately, it was the onset and progression of encephalopathy that led to the decision to proceed with LT. Given that traditional criteria for transplant, such as King's College, are difficult to apply to patients with EHS-induced ALF, we believe that patients hospitalized for EHS-induced acute liver injury (ALI)/ALF should be admitted to the intensive care unit for close monitoring especially of mental status.

The pathophysiology of EHS-induced ALI/ALF remains unclear but is believed to be related to multiple factors: (1) direct thermal damage to vascular endothelium and hepatocytes, (2) ischemic hepatitis from hypoperfusion due to shunting of blood from the splanchnic circulation to dissipate heat, (3) systemic

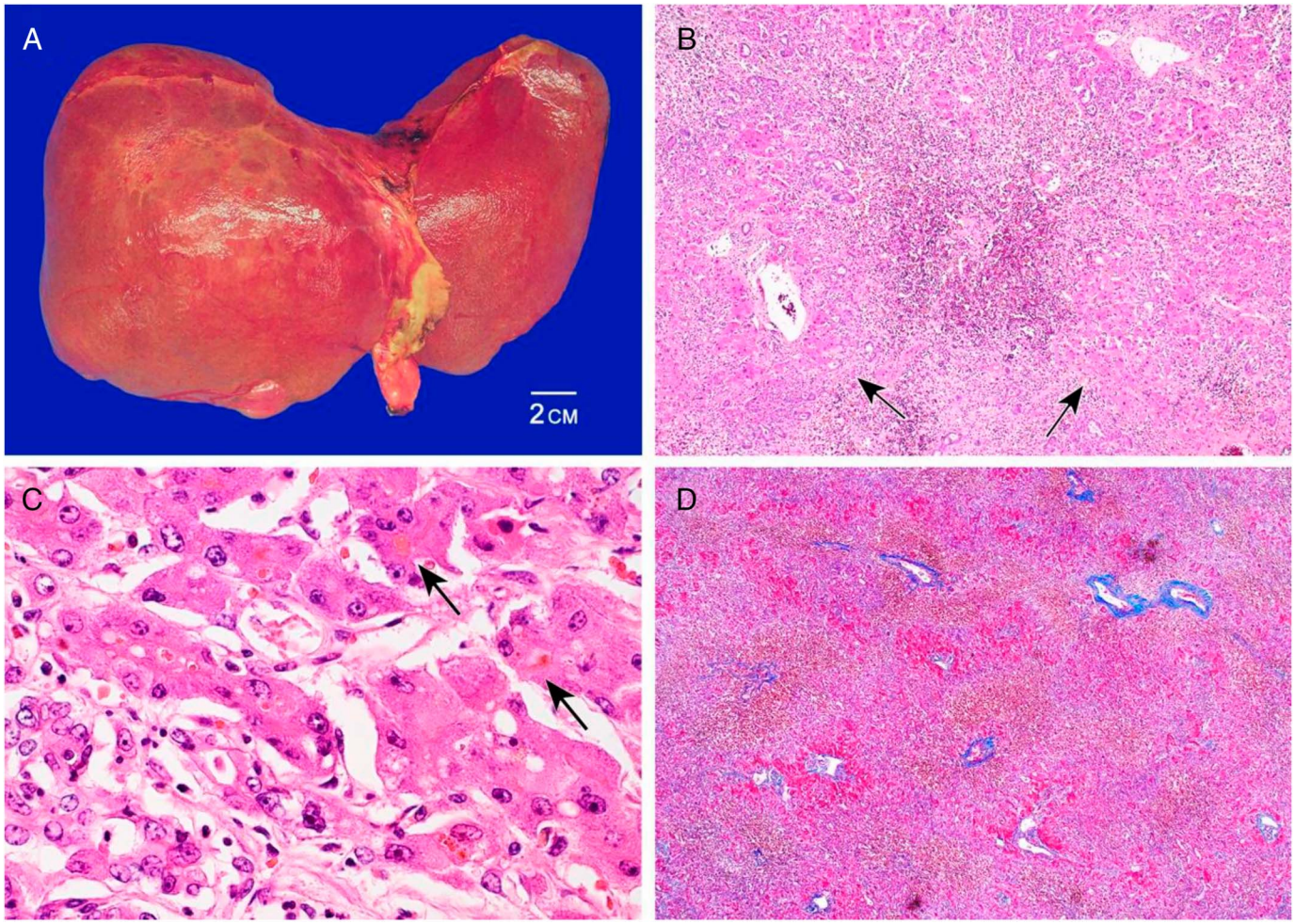

Figure 2 . Histological images of explanted liver. (A) Gross appearance of the explant. The surface shows wrinkles, which are characteristics of acute liver failure with massive hepatocytes necrosis. (B) Extensive hepatocytes necrosis involving zones 3 and 2 is present in the center. The small amount of residual viable hepatocytes (arrows) are noted around the portal triads (HES, 20×). (C) High-power view of residual hepatocytes shows degeneration with marked cholestasis (arrows) and steatosis (HES, 200×). (D) Masson trichrome stain shows no significant fibrosis, which confirms the acute process (HES, 20×). HES, hematoxylin and eosin stain.

inflammatory response syndrome leading to cellular necrosis and apoptosis, especially the activation of interleukin-1B pathway, and (4) microthrombosis.[7–9]

Our patient was given NAC, which has demonstrable benefits in acetaminophen-induced ALF, but its role in nonacetaminophen ALF remains controversial. A recent meta-analysis found that NAC significantly improved overall survival, posttransplant survival, and transplant-free survival while decreasing the overall length of hospital stay.[10] Previous studies have described the benefit of NAC primarily in patients with early hepatic encephalopathy, but the abovementioned meta-analysis did not stratify by timing of initiation of NAC.[11] Several case reports of EHS-ALI/ALF have described the initiation of NAC ranging from days 2 to 6 of admission and continued until improvement of liver function.[12–14] In 1 case report, NAC was continued until day 29 when ALT was below 500 U/L.[13] The role of NAC in EHS-ALI/ALF remains unclear, but meta-analyses and trials have found that NAC is beneficial in nonacetaminophen ALF, especially in patients with early encephalopathy.[11,15,16] In the absence of larger studies confirming efficacy, giving NAC to patients with EHS-induced ALF early is likely prudent given the relative safety of the therapeutic.

This case report demonstrates that in patients with EHS-ALI/ALF, the timing of LT can be difficult to determine. Early consideration of referral to a transplant center is warranted because EHS-induced ALF can be rapidly progressive. This case report further shows that liver transplantation can be lifesaving, particularly if performed before irreversible neurologic injury occurs. The use of standard transplant criteria for ALF is made challenging by other complications of EHS, including neurologic dysfunction and coagulopathy.

DISCLOSURES

Author contributions: JS Lin wrote the manuscript and reviewed the literature. D. Zaffar, H. Muhammad also

contributed to the manuscript writing and reviewed the literature. K. Oshima provided expert review of pathologic specimens. PS Ting, T. Woreta, A. Kim, R. Kohli, A. Cameron, B. Philosophe, S. Ottmann, R. Wesson, and A. Gurakar edited the manuscript. A. Gurakar is the article guarantor.

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