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January 2021 Critical Care Case of the Month: A 35-Year-Old Man Found Down on the Street

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History of Present Illness

A 35-year-old African-American man with a history of alcohol abuse presented to Emergency Department after he was found down. He was seen by a passerby on the street who witnessed the patient fall with a possible convulsive event. He was brought in by ambulance and was unconscious and unresponsive.

PMH, SH, and FH

The patient had a history of prior ICU admission in Yuma with septic shock secondary to a dental procedure requiring a tracheostomy in 2018. He also had a history of alcohol intoxication requiring an ED visit about 10 years ago and history of sickle cell trait. Per chart review, the patient took no home medications. Further history was unable to be obtained due to the patient's condition.

Physical Examination

On arrival the patient had a core temperature of 41°C, systolic blood pressure in the 70s-80s, heart rate of 185, respiratory rate of 19, and an oxygen saturation of 99% on room air. Patient was not able to answer any questions.

On examination, the patient had a Glascow Coma Scale of 6 (no eye response, no verbal response, and normal flexion). Pupils were 4 mm bilaterally and reactive to light. The remainder of his HEENT was unremarkable with no meningismus reported. Pulmonary exam showed rapid, shallow breathing and coarse breath sounds with no crackles, wheezes, or rhonchi. Heart examination showed tachycardia with no murmurs or extra heart sounds. Abdomen was soft and nondistended. Skin was diaphoretic without cyanosis, clubbing, or edema.

Laboratory, Radiology and EKG

Initial laboratory testing was significant for a potassium level of 7.5 mmol/L, creatinine level of 1.96 mg/dL which was increased from baseline of 0.93 mg/dL, CK level of 2344 U/L, AST 93 U/L, ALT 62 U/L, and total bilirubin 2 mg/dL. Lactic acid was within normal limits. His EKG showed sinus tachycardia. His urinalysis was cloudy with protein and blood. His head CT was negative for any intracranial abnormalities or bleed.

Hospital Course

He was given 3 L of IV fluids, empiric vancomycin and piperacillin/tazobactam, and his hyperkalemia was managed with calcium gluconate, insulin and glucose. He was intubated for airway protection due to his shallow breathing and GCS of 6, started on pressor support, and was admitted to the ICU.

Based on the initial findings, what is the ***most likely cause*** of the patient's presentation?

1. Acute encephalitis
2. Delirium tremens
3. Heatstroke
4. Malignant hyperthermia
5. Septic shock

Correct!
3. Heatstroke

This patient's clinical presentation raises high concern for heatstroke. Heatstroke is a life-threatening condition that is defined as a core body temperature usually in excess of 40°C (104°F) with associated central nervous system dysfunction in the setting of a large environmental heat load that cannot be dissipated (1). This patient was found down outside and presented with severe hyperthermia (41°C) and acute encephalopathy. This case occurred in Tucson, Arizona during a summer day with a high temperature of 43.9°C on the day the patient presented. Severe hyperthermia can cause rhabdomyolysis leading to elevated CK and hyperkalemia as seen in this patient.

Malignant hyperthermia (MH) causes high fever and tachycardia along with muscle rigidity. MH typically occurs as a reaction to anesthetic medications (halothane and succinylcholine) but heat stress can cause MH-like syndrome with rigidity and rhabdomyolysis. Acute encephalitis could explain the patient's encephalopathy, but the severe hyperthermia makes heatstroke more likely. Septic shock is also a possibility but would not explain the rhabdomyolysis. Delirium tremens can also present with fever and acute encephalopathy, especially in a patient with a history of alcohol abuse; however, blood pressure would be elevated rather than decreased as in this patient. Other differentials for this presentation include other drug intoxications (atropine, MDMA 3,4-methylenedioxymethamphetamine, cocaine), severe dehydration, lethal catatonia, serotonin syndrome, thyroid storm, neuroleptic malignant syndrome or pheochromocytoma multisystem crisis (1).

The patient was cooled with ice water and towels. His temperature improved to 38°C, heart rate decreased to the 130s, and blood pressure improved to 103/70. The patient's urine drug screen came back positive for benzodiazepines and methamphetamine. Methamphetamine may have contributed to his hyperthermia. Acetaminophen, salicylate and ethanol levels were negative. Of note, aspirin and acetaminophen are ineffective in treating heatstroke since fever and hyperthermia increase core temperatures through different physiological pathways (1).

What type of heat-related illness(es) is this patient ***most likely*** suffering from?

1. Classic heatstroke
2. Exertional heatstroke
3. Heat exhaustion
4. Both 1 and 3
5. All of the above

Correct!
4. Both 1 and 3

Heat-related illness is a set of conditions which range from milder forms to potentially fatal heatstroke. Heat exhaustion is the inability to continue activity because of environmental conditions, and is thought to be caused by a central mechanism that protects the body in times of overexertion (2). As a milder form of heat-related illness, heat exhaustion usually has core temperatures less than 104°F (40°C) and no central nervous system symptoms. If left untreated, heat exhaustion could lead to heatstroke.

Heatstroke can be categorized as classic or exertional. Classic heat stroke is due to exposure to environmental heat and poor heat-dissipation mechanisms, whereas exertional heatstroke is often associated with physical exercise and results when excessive production of metabolic heat overwhelms physiological heat-loss mechanisms (1). Classic heatstroke often affects the chronically-ill, elderly and prepubertal, who have poor heat-dissipation mechanisms. Exertional heatstroke occurs more frequently in the generally healthy, young and active, and can also occur with drug abuse due to increased metabolic demand. This patient had been exposed to high temperatures which was likely exacerbated in the setting of methamphetamine use, making it a mixed classic and exertional heatstroke picture.

Heatstroke has three phases: hyperthermic-neurologic, hematologic-enzymatic phase (peaking 24-48 hours post event), and late renal-hepatic phase. In severe cases, sustained brain injury to the autonomic and enteric nervous system can occur. Two days later, the patient was weaned off of pressor support but remained encephalopathic and required ventilator support. The patient's laboratory results are shown:

- Glucose 187 mg/dL
- BUN 33 mg/dL
- Creatinine 1.78 mg/dL
- Calcium 8 mg/dL
- Protein 5.1 g/dL
- Albumin 3.3 g/dL
- Bilirubin, total 5.9 mg/dL
- AST 4644 U/L
- ALT 2688 U/L
- Alkaline phosphatase 62 U/L

What is the ***most likely*** cause of this patient's abnormal liver enzymes?

1. Acute cholecystitis
2. Alcoholic hepatitis
3. Autoimmune hepatitis
4. Shock liver
5. Viral hepatitis

Correct!
4. Shock liver

This patient most likely has acute liver failure secondary to shock liver. Heatstroke leads to an inflammatory response similar to the systemic inflammatory response syndrome (SIRS). SIRS is mediated by circulating messenger RNA releasing cytokines and high-mobility group box 1 protein (HMGB1) with activation of leukocytes and endothelial cells. This process can result in disseminated intravascular coagulation (DIC), multiorgan failure, and death. Although it has been two days since the patient was exposed to high temperatures, multiorgan system dysfunction and failure may peak within 24 to 48 hours (1).

Viral hepatitis can also cause liver transaminases to be elevated greater than 1,000 U/L; however, this patient has suspected heatstroke and his initial presentation with severe hypotension makes shock liver more likely. Alcoholic hepatitis presents with moderately elevated liver transaminases (<500 U/L) with AST:ALT ratio >2. Ethanol levels were negative in this patient. Acute cholecystitis is unlikely as an elevation of alkaline phosphatase would be expected. Autoimmune hepatitis is a rare disorder that requires exclusion of other diseases that have a similar presentation. In this patient, shock liver is more likely.

In severe heatstroke injury, it is recommended to check liver function tests, PT/INR, ammonia, CK, LDH, myoglobin and urinalysis, CRP daily and having a low threshold for blood cultures as heatstroke can cause reduced intestinal blood flow with gastrointestinal ischemia. N-acetycysteine is recommended for acute liver failure as well as monitoring for and treating cerebral edema with 3% hypertonic saline or mannitol.

Is there an increased risk of exercise-related death in people with ***sickle cell trait?***

1. Yes
2. No

Correct
2. No

Sickle cell trait is not associated with a higher risk of exercise-related death, but it is associated with a significantly higher risk of exertional rhabdomyolysis (3). Sickle cell trait occurs in about 8 percent of the U.S. African-American population and between 1 in 2,000 to 1 in 10,000 in the Caucasian population (4). Most U.S. states test at birth but many athletes are unaware that they have sickle cell trait. The NCAA recommends that athletics departments confirm sickle cell trait status and avoid dehydration, severe exercise with acute illness, and modify training at higher altitudes (4). There is no evidence that there is an association between sickle cell trait and exertional heatstroke (1).

Later in the patient's hospital course, the patient continued to have elevated liver function tests as follow:

> Two days after admission: AST 4644, ALT 2688, Alk phos 62, Total bili 5.9
> Seven days after admission: AST 188, ALT 1440, Alk phos 85, Total bili 13.9, Direct bili 13.0.

Ultrasound of the right upper quadrant showed gallbladder wall thickening with trace pericholecystic fluid equivocal for acute cholecystitis. HIDA scan showed complete obstruction at the distal common bile duct without evidence for cystic duct obstruction. CT abdomen/pelvis showed normal liver with patent portal vein, splenic vein and superior mesenteric vein. The gallbladder was normal with radiopaque gallstones. No intrahepatic or extrahepatic biliary dilatation was noted.

What is the best explanation and management in evaluating this patient's abnormal liver function?

1. Acute acalculous cholecystitis, surgical consult for cholecystectomy
2. Ascending cholangitis, GI consult for ERCP
3. Gilbert syndrome
4. Heatstroke-induced ischemic liver injury with continued supportive care
5. Pancreatic cancer

Correct!
4. Heatstroke-induced ischemic liver injury with continued supportive care

Gastroenterology (GI) was consulted and attributed the patient's presentation and lab abnormalities to multiple acute liver injury resulting from alcohol use, drug abuse and ischemic injury with expectation that the elevated total bilirubin would slowly return to normal values. Typically shock liver causes an early rise of AST, ALT and LDH that trend down after 2 to 3 days and normalize at approximately 15 days. Total bilirubin elevation increase is seen after the AST, ALT increase and trails the resolution of the transaminases (5). Surgery was consulted and recommended clinical follow up as none of the studies showed acute acalculous cholecystitis warranting cholecystectomy. HIDA scans are most reliable for the diagnosis of acute cholecystitis compared to acute acalculous cholecystitis with sensitivity and specificity of approximately 96 percent and 90 percent respectively for acute cholecystitis (6). Ascending cholangitis is unlikely given normal alkaline phosphatase and none of the imaging showing biliary ductal dilatation. Pancreatic cancer should show a mass in the imaging studies and Gilbert syndrome presents with elevated bilirubin with elevation in indirect (unconjugated) bilirubin. Clinically, the patient's liver function tests eventually returned to normal limits without intervention and were attributed to the multiple liver injury as suggested by the GI consultant.

With supportive care, the patient's encephalopathy resolved. He was extubated and had a steady course of recovery until being discharged from the hospital.

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