Acute liver failure from low-dose acetaminophen

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Acute liver failure (ALF) is a rare, life-threatening condition defined as rapidly progressive liver dysfunction with coagulopathy (INR ≥1.5) and hepatic encephalopathy in patients without underlying liver disease.[1,2,5] In the United States and Europe, the most common cause of ALF is acetaminophen overdose.[1,3,4] While low doses of acetaminophen are generally regarded as safe, there is increasing evidence that therapeutic doses can result in ALF, especially in the setting of chronic alcohol use.[3,4,8,9] This case report explores the unique presentation of low-dose acetaminophen use as a cause of ALF and the resulting challenges in early recognition and treatment.

Case report

A 38-year-old previously healthy woman was admitted with four weeks of fatigue, progressive upper abdominal pain, and vomiting. She had been taking 3 g/day of acetaminophen for the pain for a total of 3-4 days. She reported intermittent alcohol use with increased intake the week prior to admission.

Initial lab results included AST 1900 IU/L, ALT 600 IU/L, alkaline phosphatase 80 IU/L, total bilirubin 2.5 mg/dL, and direct bilirubin 1.5 mg/dL. Lipase was elevated at 1400 IU/L. Right upper quadrant ultrasound revealed a normal common bile duct and no cholelithiasis or gallbladder wall thickening. Her presentation was thought to be alcohol-induced acute pancreatitis and alcoholic hepatitis.

On Day 2 of hospitalization, her aminotransferases significantly worsened with AST 13,200 IU/L, ALT 4100 IU/L, and total bilirubin 4.1 mg/dL. She developed coagulopathy with INR 4.4, hypoglycemia, and acute kidney injury.

The following day, her mental status deteriorated and she became encephalopathic. She was noted to have lactic acidosis and acute renal failure. She was diagnosed with acute liver failure at this time. Workup for etiology was pursued and was negative for viral infection (hepatitis A and B, EBV, and CMV), autoimmune hepatitis, or hepatic vein thrombosis. Serum acetaminophen level was undetectable though positive on urine toxicology. Etiology of ALF was considered to be acetaminophen toxicity potentiated by alcohol use.

She was started on a five-day course of IV N-acetylcysteine which resulted in drastic improvement of LFTs, coagulopathy, and mental status. She was ultimately discharged home with complete normalization of her liver function.

Discussion

This case highlights the difficulties in recognition of low-dose acetaminophen as a cause of acute liver failure (ALF) in patients with chronic alcohol use. There is increasing evidence that factors such as malnutrition and chronic alcohol use may potentiate the hepatotoxic effects of acetaminophen.[3,4,8,9] In addition, this patient presented with acute pancreatitis, a rare complication of acetaminophen-related ALF that occurs in 0.3-5% of cases, which may have distracted from early recognition of liver injury.[5] Delayed diagnosis and treatment is associated with a worse prognosis and development of multiorgan failure, such as acute renal failure, as seen in this case.[2] Therefore, the clinical suspicion for acetaminophen hepatotoxicity must remain high even in the setting of therapeutic levels of acetaminophen use.

This presentation of ALF may not initially, or ever, be recognized as acetaminophen-related. Interestingly, the most common cause of ALF in the United States following acetaminophen use is "indeterminate," or cases where an etiology was never identified.[1,2] Further, there is an increasing number of studies demonstrating that a significant number of indeterminate cases are actually due to unrecognized acetaminophen toxicity.[6,7,10] In cases of indeterminate ALF, especially in patients with any history of acetaminophen use, the administration of N-acetylcysteine should always be considered, given the clinical implications of a missed diagnosis. MM

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