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CASE REPORT | LIVER

Hyperbilirubinemia in a Patient With Sepsis: A Diagnostic Challenge

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ABSTRACT

Cholestasis due to sepsis is commonly seen in critically ill patients; however, it is often overlooked and poses a challenge in clinical diagnosis and management. In this report, we present a 29-year-old woman who presented to the emergency department with jaundice and symptoms of a urinary tract infection. Initially suspected to be Dubin-Johnson syndrome, sepsis-induced cholestasis was eventually diagnosed after testing. Sepsis should always be considered as part of the differential diagnosis while managing a patient with jaundice. The management of sepsis-induced cholestasis involves treating the underlying infection. In most cases, liver injury improves with the resolution of the infectious process.

KEYWORDS: sepsis; isolated hyperbilirubinemia; jaundice; infection

INTRODUCTION

In sepsis, hyperbilirubinemia may be caused by direct injury to the hepatocytes by bacterial products or a host response to bacterial toxins. A rise in both hepatocellular enzymes and bilirubin is frequently seen.[1] Direct hyperbilirubinemia (conjugated bilirubin >20% of total bilirubin) is the principal manifestation of cholestasis due to impaired bile formation or impaired secretion. Jaundice typically appears when serum bilirubin levels are greater than 2.5 mg/dL.[1] The incidence of hyperbilirubinemia in adults ranges from 0.5% to 54% based on multiple small retrospective studies.[1] We sought to highlight the importance of elevated bilirubin levels with normal transaminases in establishing the severity of liver dysfunction and mortality in septic patients with cholestasis, thereby preventing mortality by early diagnosis and treatment.

CASE REPORT

A 29-year-old woman with a medical history of cholecystectomy due to cholelithiasis complicated by cholangitis presented with worsening nausea, severe vomiting, nonbloody diarrhea, fever, sharp left-sided flank pain, dark brown urine, and dark stools for 1 week. She denied alcohol use, smoking, use of oral contraception, herbal supplements, over-the-counter medications, and any pertinent family history. Vitals were stable on presentation, except for elevated temperature (102.4 °F).

Physical examination was positive for mild generalized abdominal tenderness, scleral icterus, jaundice, and mild left flank tenderness. Initial laboratory tests were suggestive of an ongoing infection with cholestasis (Table 1). Urinalysis was suggestive of urinary tract infection (UTI) and notable for urobilinogen. Urine culture was negative; however, it was collected after 2 doses of antibiotics treatment, which may have caused a false-negative result. Abdominal-pelvic computed tomography without contrast was suggestive of left ascending UTI without evidence of biliary pathology. The qualitative urine Human Chorionic Gonadotropin test for pregnancy was negative. Further workup for infection, acute viral illnesses, autoimmune disorders, hemolytic disorders, and drug screen was negative (Table 1). Total urinary coproporphyrins, coproporphyrin I, and coproporphyrin III levels were normal, thus ruling out Dubin-Johnson syndrome. Calculated R factor for liver injury was 0.4, suggestive of cholestatic injury (Figure 1).[2] She was diagnosed with sepsis-induced cholestasis as a diagnosis of exclusion.

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Table 1. Laboratory test results

Laboratory test	Result	Reference range
WBC	15.9 K/mcL	4.5–11.0 K/mcL
AST	22 unit/L	5–34 unit/L
ALT	21 unit/L	0–55 unit/L
ALP	112 unit/L	38–126 unit/L
Total bilirubin	5.6 mg/dL	0.2–1.2 mg/dL
Direct bilirubin	3.2 mg/dL	0.0–0.3 mg/dL
Indirect bilirubin	2.4 mg/dL	0.1–1.0 mg/dL
CRP	28.7 mg/dL	0.0–0.5 mg/dL
ESR	115 mm/hr	0–20 mm/hr
Ferritin	728 ng/mL	20–400 ng/mL
ANA	Negative	Negative
Smooth muscle antibody	8 units	<20 units
Mitochondrial antibody	2.7 units	<20 units
Smith antibody	3 units	<20 units
Liver-kidney microsomal antibody	2.3 units	<20 units
Alpha-1 antitrypsin	292 mg/dL	90–200 mg/dL
Ceruloplasmin	47 mg/dL	18–53 mg/dL
HIV panel	Negative	Negative
Hepatitis panel	Negative	Negative
LDH	246 units/L	140–271 units/L
Haptoglobin	279 mg/dL	36–195 mg/dL

ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; WBC, white blood cell.

She was treated with fluids, ceftriaxone, and metronidazole for 5 days. Infectious symptoms resolved by day 3 and total bilirubin level normalized by day 5 of hospitalization. She was eventually discharged home on oral antibiotics for 2 days.

DISCUSSION

Sepsis associated with cholestasis is a diagnostic challenge because it necessitates the exclusion of other etiologies.[3] Intrahepatic cholestasis can be caused by viral hepatitis, alcohol hepatitis, drug-induced or toxin-induced liver injury, primary sclerosing cholangitis, primary biliary cholangitis, malignancy, pregnancy, graft-vs-host disease, sepsis, or genetic disorders, among others.[4] Various bacterial infections are associated with hyperbilirubinemia. However, gram-negative bacterial infections are most commonly implicated. In a prospective study conducted on 174 patients with sepsis-induced cholestasis, 68.6% of patients were infected with gram-negative bacteria and 31.4% with gram-positive bacteria.[5] *Escherichia coli* causing UTI and subsequent pyelonephritis was the most common pathogen.[5]

The pathogenesis of sepsis-induced cholestasis is complex and multifactorial. Multiple mechanisms may cause hyperbilirubinemia during systemic infection, including hemolysis, hepatic dysfunction, and cholestasis.[1] Lipopolysaccharides and endotoxins released by gram-negative bacteria are mainly cleared by Kupffer cells of the liver, which cause inflammation-induced cholestasis because of the production of high levels of proinflammatory cytokines such as tumor necrosis factor-α, interleukin-6, interleukin-12, interleukin-18, interleukin-1, and nitric oxide leading to altered expression and function of the transport system of bile acid.[6,7] Neutrophil recruitment to the liver in early sepsis also leads to the release of proteolytic enzymes and reactive oxygen species leading to endothelial cells and hepatocyte injury.[7] Higher levels of nitric oxide during sepsis react with lipopolysaccharides and forms free radicals, leading to vascular collapse, cholestasis, and cellular injury.[6,7]

R factor = (ALT level / Upper limit of normal ALT) / (ALP level / Upper limit of normal ALP)

To interpret the R factor, the following ranges can be used:

- R factor > 5: hepatocellular injury
- R factor between 2 and 5: mixed injury
- R factor < 2: cholestatic injury

Figure 1. R factor and interpretation of the results of R factor.[2] ALT, alanine aminotransferase; ALP, alkaline phosphatase.

The Sequential Organ Failure Assessment score, Multiorgan Dysfunction Score, and Logistic Organ Dysfunction System score recommended by the International Sepsis Definitions Conference use bilirubin levels as an indicator for liver dysfunction, except for the Logistic Organ Dysfunction System that incorporates the international normalized ratio value in addition to bilirubin levels.[8] Early increase in plasma bilirubin level >2 mg/dL is a widely used biomarker and a strong independent risk factor of mortality in patients with sepsis.[7] In a prospective study of 608 patients, mortality was found to be significantly higher in patients with sepsis-induced cholestasis (10.6%) compared with patients with sepsis without cholestasis (1.5%).[3] A retrospective study on the influence of hyperbilirubinemia on long-term outcome in 2,784 patients with sepsis demonstrated that in-hospital mortality was significantly higher (16.2%) in patients with bilirubin levels >2 mg/dL compared with patients with low bilirubin levels, and the 1-year mortality rate was 1.6 times higher for patients with bilirubin levels >5 mg/dL[9]

If the patient has hyperbilirubinemia along with elevated alanine transaminase and aspartate transaminase levels, hepatocellular causes of abnormal liver function tests should be considered, including viral hepatitis, acetaminophen toxicity, hepatic ischemia, and toxins (Figure 2).[1,10–12] In patients who develop hyperbilirubinemia with normal aspartate transaminase and alanine transaminase in the setting of infectious symptoms, minimum workup should include urine analysis, blood cultures, urine cultures, and chest x-ray to identify a source of infection. If an infectious etiology cannot be readily identified, further testing should be performed to determine the causes.[1] There are no specific guidelines for the management of liver dysfunction in sepsis; however, early goal-directed fluid

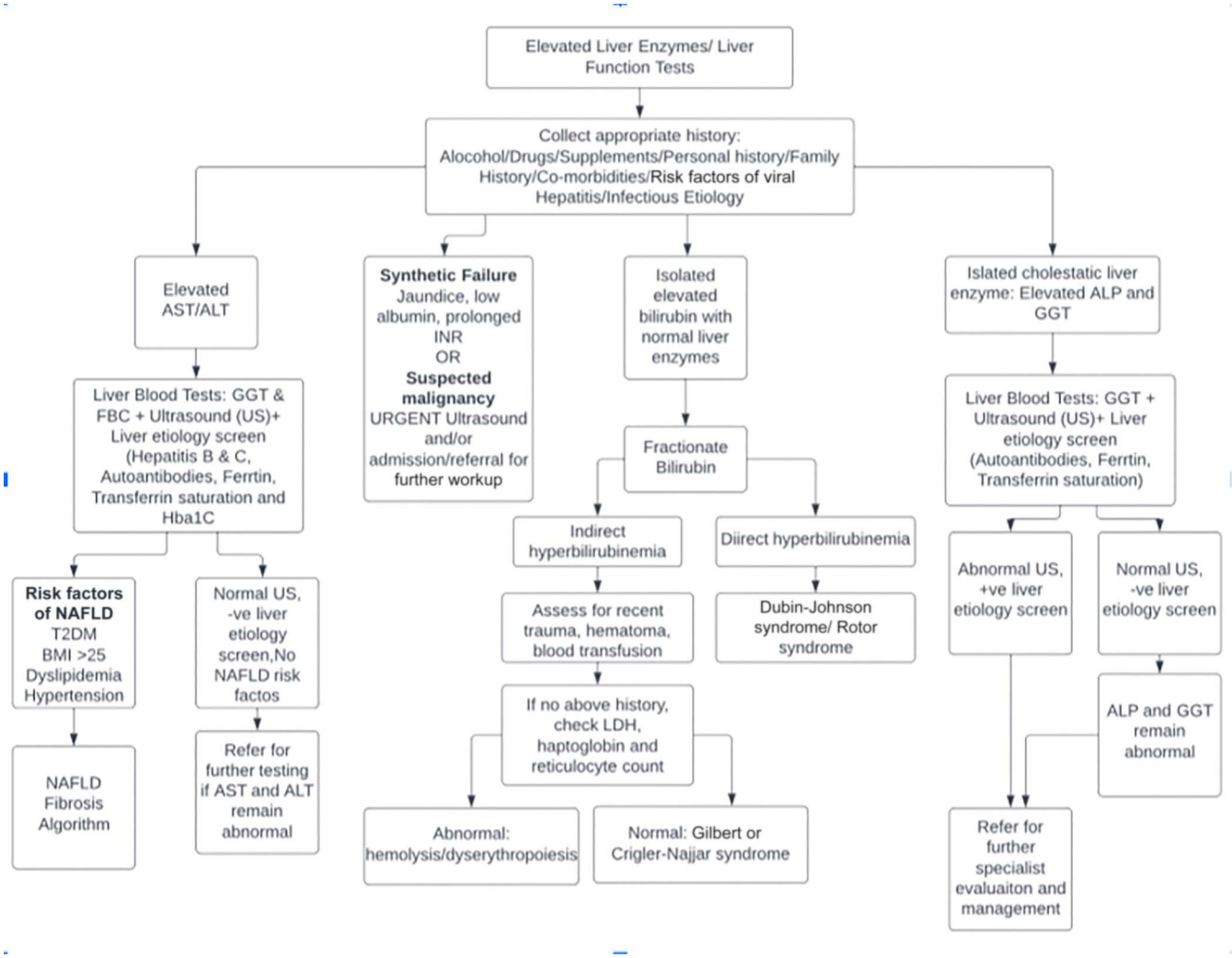

Figure 2. Workup for abnormal liver blood tests.[10,12] ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index ; FBC, full blood count; GGT, gamma-glutamyl transferase; INR, international normalized ratio; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio.

resuscitation, early initiation of antibiotics to control the source of infection, and vasopressor support for optimal organ perfusion may minimize or prevent liver injury.[8] For hemodynamically stable patients, early enteral feeding is associated with decreased infection rates and metabolic complications. It also prevents cholestasis by promoting resurgence of the enterohepatic cycle and bile acid secretion.[8]

The limitation of the case is the delay in the collection of the urine culture leading to false-negative results. Tools and markers to diagnose early liver dysfunction in patients with sepsis are warranted in the future to evaluate for newer therapeutics and eventually improve the prognosis of sepsis.

DISCLOSURES

Author contributions: All authors contributed to the study's conception and design. Patient consent was obtained by YR Shah. Clinical care was provided by YR Shah and P. Chitagi. Material preparation was provided by LG Rabinowitz and DS Dahiya. The first draft of the manuscript was written by YR Shah, and all contributors commented on the previous version of the manuscript. All authors read and approved the final manuscript. YR Shah is the article guarantor.

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