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Blue Liver: Case Report of Blue Liver

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Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Male, 39-year-old
Final Diagnosis: Hepatotoxicity
Symptoms: Jaundice
Medication: —
Clinical Procedure: Cholecystectomy
Specialty: Gastroenterology and Hepatology • Surgery

Objective: Unknown ethiology

Background: Although many cases of unusual liver discoloration exist, such as blue liver syndrome which is linked to oxaliplatin-based chemotherapy, our finding was seen in a patient who was not on chemotherapy. A 39-year-old male who presented with jaundice was found to have blue liver discoloration.

Case Report: A 39-year-old male presented with jaundice of one-month's duration evidenced by elevated total and direct bilirubin. An ultrasound and magnetic resonance cholangiopancreatography (MRCP) demonstrated thickened gall bladder wall but no common bile duct stones. A robotic-assisted laparoscopic cholecystectomy with liver biopsy was performed. Intraoperatively, the liver was noted to be unusually blue in color. During his postoperative course, the patient developed excessive incisional bleeding associated with an increase in international normalized ratio (INR) and increasing direct hyperbilirubinemia. This was managed with blood transfusions, and ursodeoxycholic acid was begun, which resulted in improvement of his bilirubin levels and overall recovery.

Conclusions: Drug induced cholestasis and liver injury is a common cause of elevated liver enzymes. However, the unusual blue appearance of the liver should prompt an evaluation for other unusual and rare causes of obstructive jaundice.

MeSH Keywords: Drug-Induced Liver Injury • Genes, MDR • Hyperbilirubinemia

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Background

Although many cases of abnormal liver discoloration exist, as in the case of blue liver syndrome, which is associated with oxaliplatin-based chemotherapy, our finding was seen in a patient who was not on any type of chemotherapy [1]. Abnormal liver function enzymes are common laboratory finding that physicians in general, and surgeons in specific, see routinely in their practice. Many of these findings can be attributed to a specific underlying condition or medication that may have caused this – although a significant percentage remains idiopathic. Medication induced hepatotoxicity may be a subtle, often underrated cause of abnormal hepatic function enzymes.

Combining multiple medications may increase the risk of hepatotoxicity [2], as some studies have shown in the case of proton pump inhibitors used with chemotherapeutic agents [3,4], which should be noted during history taking.

Case Report

A 39-year-old male, with no previously known medical illnesses, presented to the Emergency Department with painless obstructive jaundice over a 4-week duration. He had lost approximately 13.6 kg (30 lb) since these symptoms began due to a loss of appetite. His primary care physician noticed that his symptoms began 10 to 14 days after starting oral clotrimazole troche, 10 mg, 5 times daily for oral thrush. He reported no other medications or herbs ingestion at that time, and he had no known drug allergies. The medication was then discontinued, and a workup was done by his primary care physician. His bilirubin increased from 14 to 21 mg/dL during that period of time. He denied any alcohol or illicit drug use and had not experienced any pain, nausea, vomiting, fevers, or chills. No history of liver disease in the family was reported. His laboratory workup showed mild transaminitis, with alanine aminotransferase (ALT) 185 U/L (reference range: 0–69), aspartate aminotransferase (AST) 66 U/L (reference range: 0–50), alkaline phosphatase (ALP) 150 U/L (reference range: 38–126), international normalized ratio (INR) was 1.2, prothrombin time (PT) 13.6 seconds (reference range: 10.4–15), activated partial thromboplastin time (aPTT) was 39 seconds (reference range: 22–38), C-reactive protein (CRP) was less than 0.5 mg/dL (reference range: 0–0.8), while no erythrocyte sedimentation rate (ESR) was obtained. Hemoglobin was 15.5 g/dL (reference range: 12.7–17.8), hematocrit of 45.4% (reference range: 39–50), white blood cells (WBCs) 5.5 K/mcL (reference range: 3.3–11.5) and platelets of 321 K/mcL (reference range: 150–450). Lipase was mildly elevated at 258 U/L (reference range: 0–200). A hepatitis panel as well as autoimmune hepatitis markers were negative for hepatitis B surface Ag, hepatitis B core IgM, hepatitis C IgM, hepatitis E IgG, hepatitis A IgM, tissue transglutaminase IgG, anti-smooth muscle IgG, and anti-mitochondrial IgG antibodies. Based on the recommendations of our gastroenterology and hepatology colleagues, no further testing, including other viral or genetic studies, were necessary at that point.

On physical examination, the patient was alert and oriented to time, place, and person, in no acute distress, and was noted to be jaundiced with scleral icterus without palpable hepatomegaly, abdominal distension, or upper abdominal tenderness. An abdominal ultrasound performed on admission demonstrated the presence of sludge (Figure 1).

Magnetic resonance cholangiopancreatography (MRCP) showed cholelithiasis and a thickened wall of the gallbladder, consistent with cholecystitis, as well as focal pancreatitis with no biliary obstruction or dilatation (Figure 2). The common bile duct size was 4 mm.

Giving the radiologic findings which were consistent with cholecystitis, and the need for liver biopsy, the patient was offered a minimally invasive cholecystectomy with liver biopsy as

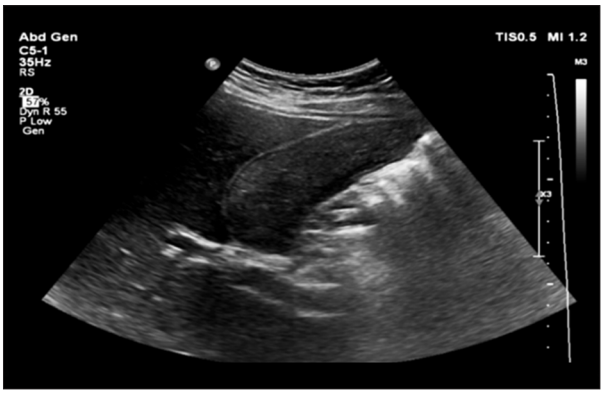

Figure 1. Ultrasound image showing gallbladder filled with sludge. No discrete shadowing gallstones or polyps were visualized on ultrasound.

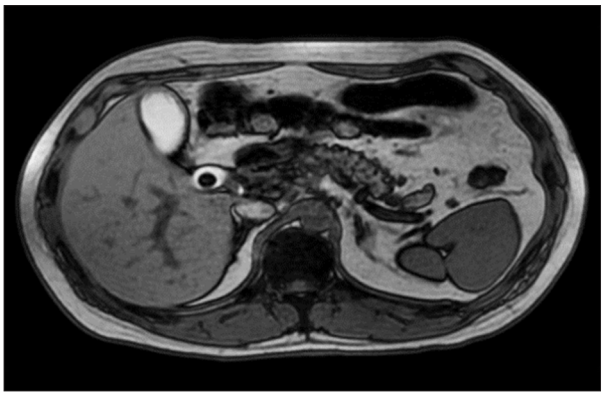

Figure 2. Magnetic resonance imaging showing thickening of the gallbladder wall without bile duct obstruction. This finding points to acute cholecystitis.

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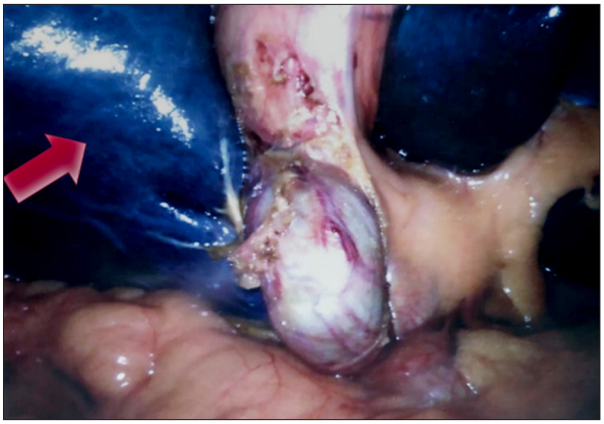

Figure 3. Intra-operative laparoscopic image demonstrating the blue color of the liver. Note the normal color of surrounding tissues.

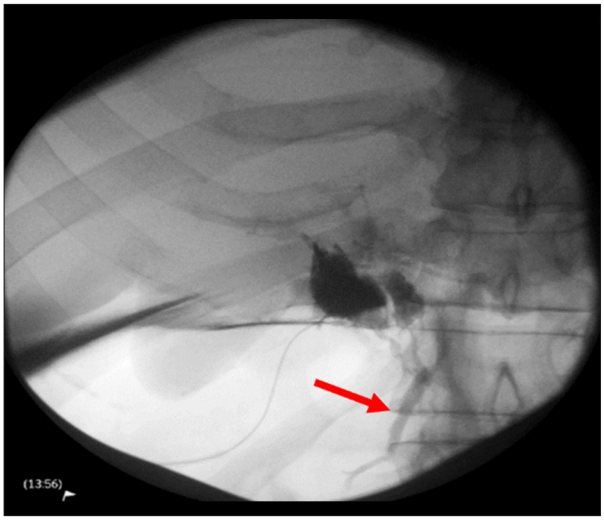

Figure 4. Intra-operative cholangiogram showing a patent common bile duct (arrow) without stones.

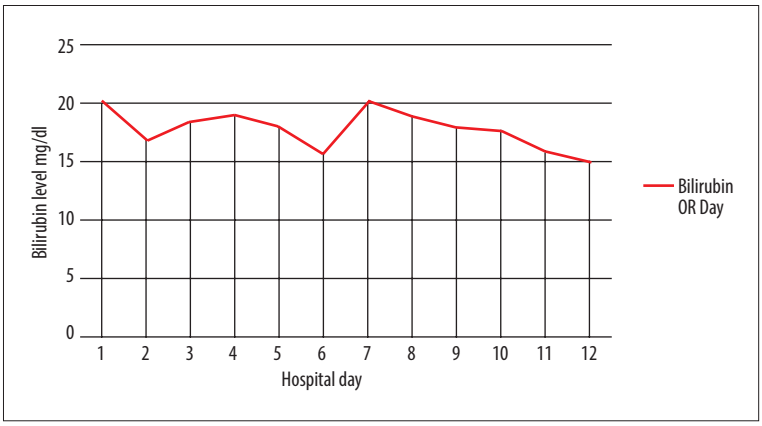

Figure 5. initiating ursodeoxycholic acid slowly and continued to improve over the next month of outpatient follow up.

a diagnostic and possible therapeutic procedure. The patient underwent a robotic-assisted laparoscopic cholecystectomy with intraoperative cholangiogram and liver biopsy. Upon entry into the abdomen, the entire liver was found to have a blue discoloration (Figure 3). As for the cholecystectomy and cholangiogram, they were both performed without complications (Figure 4).

Post-operatively, the total bilirubin, with fractionation showing direct hyperbilirubinemia, progressively decreased after the initiation of ursodeoxycholic acid during the period of hospitalization (Figure 5).

On post-operative day 3, he developed excessive incisional bleeding associated with elevation in the INR of 4.6 and a hemoglobin drop to 6.5 mg/dL. A transfusion of packed red blood cells and fresh frozen plasma was performed, which normalized his INR and the incisional bleeding ceased.

The pathology examination of the gallbladder specimen indicated chronic cholecystitis with fibrosis of the muscularis propria. The liver biopsy showed marked cholestatic hepatitis with hepatocanalicular biliary stasis, abundant bile plugging within bile canaliculi and lack of pigmented hepatocytes. Iron stain revealed minimal iron in 10% of hepatocytes and there was no cirrhosis or fibrosis on the Trichrome stain (findings shown in Figure 6). The findings did not identify a specific etiology but suggested possible causes as an adverse drug toxic effect, acute viral infection, or progressive familial intrahepatic cholestasis, specifically type III which is associated with multidrug resistance protein 3 (MDR3) deficiency.

As aforementioned, a viral hepatitis profile did not show any evidence of viral infection. A genetic test was performed looking for MDR3 deficiency, specifically *ABCB4* gene, showing no evidence of mutation in this gene.

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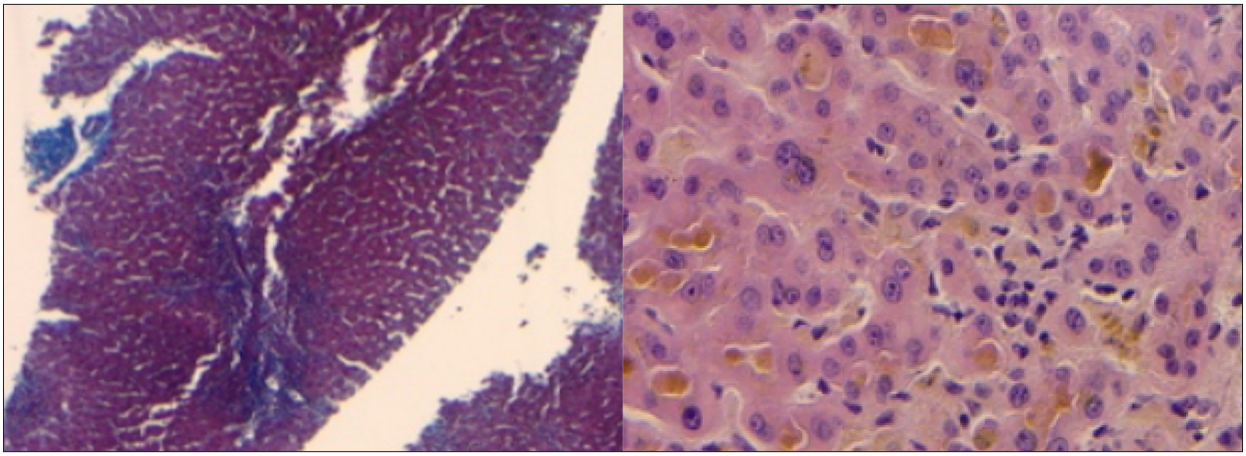

Figure 6. Abundant bile plugging is seen within the bile canaliculi. Iron stain reveals the presence of minimal iron within the hepatocytes. Trichrome stain reveals no evidence of fibrosis or cirrhosis.

The patient was discharged home on post-operative day 7. At 1 month, his total bilirubin level had decreased to 2.3 mg/dL without additional interventions.

Discussion

Since the liver is the main source of drug metabolism, it is one of the first organs to be directly injured by a drug or its toxic metabolites [5]. Therefore, drug induced hepatotoxicity is considered a major cause of acute liver injury.

Drug induced liver injury can present as an acute hepatitis or cholestasis, which are both described as possible side effects of antifungals [6–9]. Those side effects usually respond to withdrawal of the medication, although some more severe cases leading to liver failure and transplantation have been described. Thus, a close follow-up of patients who are on antifungals, with prompt cessation of the drug if any signs of hepatotoxicity arise, is of absolute importance.

Although all antifungals can cause hepatotoxicity or intrahepatic cholestasis, Rodriguez et al. (1999) found an increased risk with the use of itraconazole and ketoconazole [6].

It is imperative to mention that familial intrahepatic cholestasis predisposes the patient to cholestasis and hyperbilirubinemia when exposed to some drugs. Underlying chronic liver disease is also a risk factor for developing azole-induced hepatotoxicity [10]. Therefore, obtaining a good family history can aid in finding such unusual diseases. In our case, type 3 familial intrahepatic cholestasis, also known as multidrug resistance protein 3 (MDR3) deficiency [11,12], was a suggestion based on the pathology findings, but was then ruled out by genetic testing.

Of interest, even without a germline mutation of the *ABCB4* gene causing MDR3 deficiency, cases of clotrimazole and other drugs causing inhibition of MDR3 activity resulting in liver damage have been also described [13,14].

The precise reason of the liver's blue discoloration is unknown. Although the literature consists of a number of papers that use the description of "blue liver syndrome", this disease entity (which is also known as sinusoidal obstruction syndrome (SOS), toxic sinusoidal injury, or veno-occlusive disease) is a vascular pattern of drug induced injury which has been associated with oxaliplatin-based chemotherapy [15]. In this case, the patient had not been on chemotherapy to suggest such diagnosis.

Conclusions

Drug induced cholestasis is a common side effect to a large number of drugs. It should be considered in cases of unexplained elevated liver enzymes. A good history and physical examination can aid in the diagnosis. Exclusion of other more common etiologies is needed. Therefore, a combination of laboratory tests, liver histology, and genetic studies may be helpful in establishing the diagnosis.

We report a case of hepatic cholestasis with blue liver which possibly resulted from an antifungal medication.

Conflict of conflicts

None.

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