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Prolonged cholestasis due to hepatitis A virus infection in a young adolescent male with a known case of hemoglobin E disease: early response to steroid therapy

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Background: Acute hepatitis due to hepatitis A virus infection is a self-limiting mild disease. Sometimes, it may have an atypical course in few percentages. We reviewed with characteristics, response to steroid therapy, and outcome of prolonged cholestatic jaundice in hepatitis A virus infection.
Case summary: We analyzed acute hepatitis with a prolonged cholestatic course due to hepatitis A virus infection in an adolescent with preexisting hemoglobin E disease. Bilirubin was gradually increasing, the maximum total bilirubin was 48.3 mg/dl, and direct 46.6 mg/dl at day 50 of symptoms onset. After that, the steroid was started along with ursodeoxycholic acid. The patient gradually improved clinically and biochemically. **Conclusion:** Hepatitis A virus infection may cause prolonged cholestatic severe jaundice in a patient with preexisting congenital hemolytic disease. Steroid therapy may induce early recovery.

Keywords: acute viral hepatitis, severe jaundice, hemolytic disease, prednisolone therapy, alanine aminotransferase, case report

Introduction

The age of the host affects how the hepatitis A infection presents clinically. Less than 30% of infected young children displayed symptomatic hepatitis, but over 80% of infected adults displayed severe acute hepatitis and had noticeably raised blood aminotransferase levels (1). Atypical manifestations included relapse, cholestasis, rash, arthralgia, and hematological abnormality that may occur in hepatitis A virus infection (2). According to the literature, this manifestation only happens at a rate of 0.4–0.8% (3) and is quite infrequent. Hepatitis A virus, however, can also rarely impact kidneys and other tissues such as muscles, skin, lymph nodes, and skin. When the hepatitis A virus is acutely infected, numerous hematological symptoms have been documented. Hemolysis is among them (4). In patients with hepatitis A virus infection, hemolysis is the most frequent hematologic abnormality to appear. The lack of glucose-6-phosphate dehydrogenase and autoimmune hemolysis in this syndrome has been hypothesized as etiologies for the hemolysis of red blood cells. Other hepatitis A virus-related hematological issues include aplastic anemia, immune thrombocytopenia, and pure red cell aplasia (5). In this case report, the patient had hemoglobin E disease that presented with prolonged cholestatic hepatitis along with hemolysis due to hepatitis A virus infection that responded to prednisolone therapy.

Case presentation

Chief complaints: A 20-year-old adolescent male came from a hill tract area that presented with jaundice, anorexia, and weight loss for 7 weeks.

History of present illness: According to the patient's statement, he was reasonably well 7 weeks back. Then, he developed jaundice which became progressively deepened over 7 weeks. He also developed anorexia and weight loss during this illness. All these symptoms were preceded

by fever for 5 days during the onset of the illness. However, he had no significant pruritus. His initial viral markers were negative, and malaria was excluded. He was treated with ursodeoxycholic acid (UDCA, 300 mg twice daily) and blood transfusion when hemoglobin was 9.5 gm/dL without any success. As his condition did not improve, rather was deteriorating, he was admitted to the gastroenterology department of Apollo hospital Dhaka through the emergency department at 7 weeks of illness for further evaluation and management.

History of past illness: He was diagnosed with a case of hemoglobin E disease for the last 2 years, and his bilirubin was around 3 mg/dL, Hb around 10 gm/dL for the last 2 years, and no previous history of blood transfusion, drug ingestion, or similar severe episodes of jaundice.

Physical findings: At admission, he was conscious, oriented, mildly pale, vitally stable, deeply icteric, liver palpable 4 cm, and spleen palpable 5 cm.

Laboratory findings: His laboratory reports in the emergency department showed that the total bilirubin was 48.3 mg/dL, direct bilirubin was 46.6 mg/dL, lactate dehydrogenase (LDH) was 140 U/L, alanine aminotransferase (ALT) was 36 U/L, aspartate aminotransferase (AST) was 92 U/L, alkaline phosphatase (ALP) was 111 U/L, gamma-glutamyl transferase (GGT) was 60 U/L, albumin was 2.6 gm/L, and DIC profiles revealed normal. His hemoglobin was 12.9 gm/dL, total leukocyte count was 9.72 × 103, platelet count was normal, reticulocyte count was 7.24%, peripheral blood film showed microcytic hypochromic anemia, and direct Coombs test was negative. After admission, the patient was evaluated thoroughly both clinically and by appropriate investigations.

To find out the etiology of cholestatic jaundice autoimmune markers, antimitochondrial antibody and ceruloplasmin were performed, and all were normal (**Table 1**). The reticulocyte count was 7.5% and LDH was 125 U/L on the repeated result. All the viral markers and hemoglobin electrophoresis were repeated.

Imaging findings: MRCP was done, and the findings were normal. Fibro scan showed FSS 15.9 kPA.

Genetic study: Viral genotyping was not performed as it was not available.

Expert consultation: Hematological consultation was taken by Prof. Col. Dr. Md. Moniruzzaman, MBBS, MCPS (Clinical Path), FCPS (Hematology) as per his hemoglobin disease.

Final diagnosis

Prolonged cholestatic jaundice due to acute hepatitis A virus infection with hemoglobin E disease.

TABLE 1 | Investigations to diagnose and exclude of etiology of cholestatic jaundice and complications.

Investigations	Findings
ANA	Negative
Anti SM IgG	Negative
Anti-mitochondrial antibodies	Negative
USG of W/A	Splenomegaly
MRCP	Normal intrahepatic and extrahepatic biliary channels hepatosplenomegaly
Hb Electrophoresis	Hemoglobin E disease
Anti-HAV IgM	Positive
Anti HEV IgM	Negative
HBsAg	Negative
Anti-HBc IgM	Negative
Anti-HBs	Positive
Anti-HCV	Negative
Coombs test	Negative
Creatinine	Normal
Electrolytes	Normal
PT, INR	15 s, 1.28

Treatment

The patient and his parents were counseled. Prednisolone was started on day 3 of admission 40 mg per day along with ursodeoxycholic acid, antioxidants, and other nutritional supportive care. The bilirubin level was gradually reducing. Then, prednisolone was continued at 40 mg per day for 2 weeks. later, the patient was discharged with gradual tapering of prednisolone over 3 weeks until bilirubin 5 mg/dL. The patient is still asymptomatic at follow-up, 3 months after beginning the steroid medication, and there are no biochemical or clinical signs that a relapse has occurred (**Figure 1**).

Outcome and follow-up

The patient becomes symptoms free and with no relapse at 3 and 4 months follow-up.

Discussion

Our patient, a 20-year-old male, presented with prolonged cholestatic jaundice due to hepatitis A virus infection. He was already a known case of hemoglobin E disease without any need for a previous blood transfusion. This atypical presentation made the patient and parents anxious and increased morbidity and medical cost. Therefore, appropriate diagnosis and treatment were needed. There are few case reports of prolonged cholestatic course in acute hepatitis

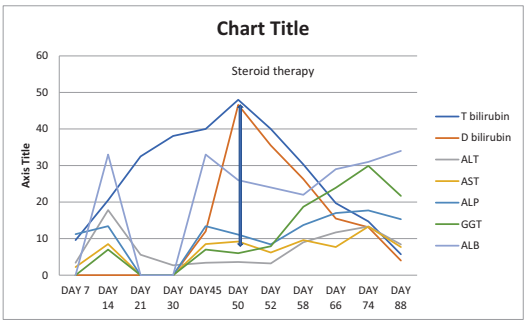

FIGURE 1 | Serum biochemistry of patient (ALT, alanine aminotransferase 1×10 U/L; AST, aspartate aminotransferase 1×10 U/L; ALP, alkaline phosphatase 1×10 U/L; GGT, gamma-glutamyl transferase 1×10 U/L; ALB, albumin gm/L).

A virus infection (6–8). Prolonged cholestasis is defined as raised total bilirubin > 5 mg/dl with direct bilirubin more than 50% persisting more than 4 weeks after diagnosis (9). Although previously it was bilirubin > 10 mg/dl that persisted for at least 12 weeks, it was shortened to reduce morbidity and medical cost. The clinical features of prolonged cholestasis of hepatitis A virus infection are jaundice, dark urine, pruritic skin, diarrhea, and weight loss (1). Our patient also presented with deep jaundice, dark urine, weight loss, and mild pruritus but no diarrhea. At the time of admission, his bilirubin was 48.3 mg/dl; direct was 46.6 mg/dl. His reticulocyte counts were 7.5%, and the Coombs test was negative. Hemolysis is an atypical feature of hepatitis A virus infection. Glucose-6-phosphate dehydrogenase deficiency and autoimmune hemolysis are the etiologies for hemolysis of red blood cells in this condition (10–12). Aplastic anemia, immune thrombocytopenia, and pure red cell aplasia are the other reported hematological problems of the hepatitis A virus (13, 14). The presenting case has mild hemolysis possibly due to the presence of hemoglobin E disease. This is the first case report of prolonged cholestasis in acute hepatitis A virus infection which is a case of hemoglobin E disease. The exact etiology of prolonged cholestasis is not known. Coinfection with the two sub-genotypes of the hepatitis A virus may account for the severe and prolonged course of the illness. Sometimes, severe cholestatic hepatitis due to hepatitis A virus infection occurs when concomitant with other hepatotropic virus infections (5). Genotyping of the hepatitis A virus had not been done due to the unavailability of the test in our center. Some case reports of prolonged cholestasis in hepatitis A virus infection showed that corticosteroid along with choleretic agents has synergistic actions and prompt recovery occurred (6–8, 11, 13). Ursodeoxycholic acid stimulates the glucocorticoid receptor as well as the normal and alternate efflux pathways for bile salts, highlighting the need for their combined use for maximum response. Corticosteroids eliminate cholestasis by inhibiting inflammation and by stimulating the alternate efflux pathway for bile salts (15). In this case report, after starting corticosteroids, bilirubin dramatically reduced and gradually tapered steroid. After withdrawing steroids, the patient maintains a normal bilirubin level without relapse.

Conclusion

Prolonged cholestatic severe illness may occur in acute hepatitis A virus infection in a patient with preexisting hemolytic disease. Corticosteroids along with ursodeoxycholic acid greatly reduced the bilirubin level, caused early recovery, alleviated the anxiety of patients, and reduced hospital course. To see the benefits of steroids to alleviate prolonged cholestasis due to hepatitis A virus infection, a randomized case-control study is needed.

Author contributions

LC designed the report and approved the manuscript. AY collected the patient's clinical data, analyzed the data, and wrote the manuscript.

Informed consent statement

Consent was obtained from the patient.

Institutional review board statement

This study was approved by the coordinator of the department and did not require IRB approval.

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