

# Hepatitis A-Associated Cholestasis and Aplastic Anemia

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## Abstract

Hepatitis A virus (HAV) infection in children is typically an acute, self-limited illness associated with general, nonspecific symptoms. Prolonged cholestasis is a rare atypical form of HAV infection that is characterized by serum bilirubin levels higher than 10 mg/dl for more than 12 weeks. Aplastic anemia is another very rare complication of HAV. We report the case of an 11-year-old male with blood group O Rh positive who developed cholestasis followed by aplastic anemia postfulminant HAV infection. Liver function tests rapidly responded to a short course of steroid treatment. The patient had a sickle cell trait and a variant of ABCB11 gene. There was no history of traditional herbal treatment, but we noticed several cautery marks. Immunosuppressive medication was started for aplastic anemia, and he is listed for urgent bone marrow transplant. This is the first reported case of prolonged cholestasis followed by aplastic anemia complicating fulminant HAV infection in a Libyan adolescent.

**Keywords:** Aplastic anemia, cholestasis, hepatitis A

## INTRODUCTION

Hepatitis A virus (HAV) infection in children is typically an acute, self-limited illness associated with general, nonspecific symptoms, such as fever, malaise, anorexia, vomiting, nausea, abdominal pain or discomfort, and diarrhea. During the prodromal period, aminotransferases are typically elevated. Jaundice usually occurs 1 week after the onset of symptoms, along with dark urine and mild hepatomegaly, and lasts for <2 weeks with no complications.<sup>[1]</sup>

Prolonged cholestasis is a rare atypical form of HAV infection that is characterized by serum bilirubin levels higher than 10 mg/dL for more than 12 weeks. Aplastic anemia is another very rare complication of hepatitis A virus (HAV).<sup>[2,3]</sup>

We report one case of cholestasis and aplastic anemia following fulminant HAV infection in an 11-year-old Libyan male.

## CASE REPORT

### History and physical examination

An 11-year-old male was transferred to the Department of Paediatric Gastroenterology and Hepatology, University Hospital, Tripoli, Libya, in November 2018 with a history of itching and prolonged jaundice for 3 months post

HAV infection (positive HAV IgM). He is a product of nonconsanguineous parents at term with uneventful vaginal delivery and received all vaccination according to Libyan schedule. He has two healthy sisters and one brother. There was a family history of two abortions, and no history of traditional herbal remedy or travel abroad recently or hematological or chronic liver diseases. On admission, he was deeply jaundiced with no signs of chronic liver disease, but with cautery marks. The liver was palpable (right lobe 1 cm below the costal margin and left lobe 3 cm below the costal margin). The spleen was not palpable, and there was no ascites. The respiratory, cardiovascular, and central nervous systems were normal.

### Investigations

Initial investigations revealed a normal leukocyte count and hemoglobin level, low platelet count, prolonged prothrombin

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time and international normalized ratio, hyperbilirubinemia mainly direct with high serum transaminases, bile acids, and plasma ammonia [Table 1]. Viral screen and screening for Wilson's disease and autoimmune hepatitis were all negative. Abdominal ultrasound scan revealed an increased periportal echogenicity of liver with normal intrahepatic biliary radicals and edematous gallbladder with a thickened wall. The common bile duct, spleen, and both kidneys were normal with no evidence of free intraperitoneal fluid.

### Management and progress

The patient was managed with low-protein diet, regular fresh frozen plasma, ursodeoxycholic acid, lactulose, and neomycin orally and a short course of oral prednisolone (1 mg/kg/day). The coagulation profile returned to normal, and liver enzymes and bilirubin started to decline. The patient was sent home for follow-up. After 1 week of discharge, the patient came back to the hospital with epistaxis, severe mouth thrush, and gum bleeding interfering with swallowing. He was readmitted to the hospital and treated with systemic antifungal (intravenous fluconazole) with rapidly tapering course of steroids. Within this time, the result of hemoglobin electrophoresis showed sickle cell trait, and complete blood count showed pancytopenia. White blood cell count was low at  $2.8 \times 10^3$ , hemoglobin concentration was 9 g/dl, and platelet count was  $9 \times 10^3$  with prolonged bleeding time. Bone marrow aspiration and biopsy results were consistent with aplastic anemia [Figure 1]. The patient was referred to the pediatric hematology department, where he received steroids, cyclosporine, regular packed red blood cells, and platelet transfusions. He is on the waiting list for bone marrow transplant at the time of preparation of this case report.

**Table 1: Investigations on admission and after 3 weeks**

Investigation	On admission	Three weeks later
WBC count	$4 \times 10^3$	$6.7 \times 10^3$
Hemoglobin (g/dl)	12.2	7.8
Platelet count	$98 \times 10^3$	$62.4 \times 10^3$
Reticulocytes (%)	1	0
Prothrombin time (s)	39.1	14.9
PTT (s)	42.7	30.4
INR	6.4	1.25
Total bilirubin (mg/dl)	26.9	18.48
Direct bilirubin (mg/dl)	24.2	-
ALT (U/L)	1593.7	492.9
AST (U/L)	2008.7	374.7
GGT (U/L)	105	-
ALP (IU/L)	393	-
Total plasma protein (g/dL)	7.34	7.57
Serum albumin (g/dL)	3.7	5.2
Plasma ammonia ( $\mu\text{mol/l}$ )	101	59
Bile acids ( $\mu\text{mol/l}$ )	916	-

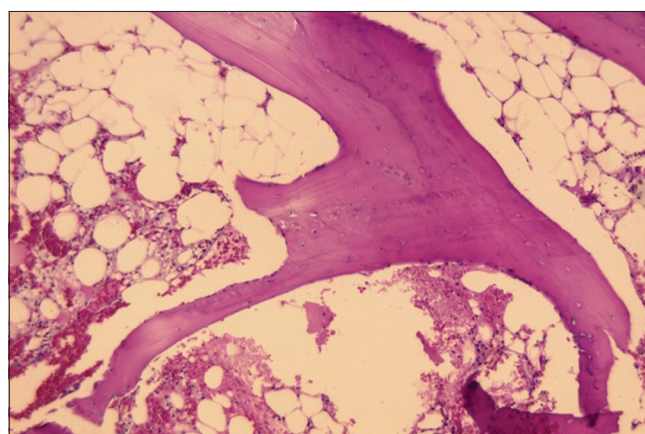
WBC: White blood cell, PTT: Partial thromboplastin time, INR: International normalized ratio, ALT: Alanine amino transferase, AST: Aspartate aminotransferase, GGT: Gamma glutamyl transferase, ALP: Alkaline phosphatase

## DISCUSSION

HAV, an RNA unenveloped single-stranded virus, is primarily transmitted from person to person via the fecal–oral route and through contaminated water and food such as shellfish and uncooked vegetables or fruit prepared by infected food handlers. The virus is present worldwide, but the level of prevalence depends on local sanitary conditions; HAV circulates widely in populations living in area with poor sanitation infrastructure. In the majority of cases, the infection is asymptomatic; very few may have symptoms ranging from mild to severe and lasting few days to several months. A previous study from Libya showed positive IgG antibodies against HAV in all children studied by the age of 7 years.<sup>[1]</sup>

Cholestatic jaundice and liver function abnormalities in the present patient rapidly responded to steroid treatment followed by rapid tapering because of other complications. Patients with sickle cell disease, uremia, and glucose-6-phosphate dehydrogenase deficiency may have increased risk of HAV infection.<sup>[2]</sup> Gokce considered that patients who are prone to hemolysis or those who have hemolytic disease may be more susceptible to cholestatic form of HAV infection.<sup>[3]</sup> In line with this, our patient has a sickle cell trait.

Genetic studies showed that two procholestatic polymorphisms, ABCB11 and ABCB4, within the hepatocanalicular transporter may contribute to a more pronounced course of HAV infection;<sup>[3]</sup> however, next-generation sequencing analysis of ABCB11 and ABCB4 genes (Bioscientia, institute for medical diagnostics, Germany) in our patient detected a new variant of ABCB11, c.3697A>G.p.(Ile1233Val), chr.2.1669781235, heterozygous that has not been reported before. As mild hematologic manifestations may accompany acute viral hepatitis, including moderate, transient depression of one or more of the peripheral hematopoietic elements, we considered the thrombocytopenia in the early investigations of our patient as a mild complication of HAV infection. A short course of steroid besides inducing a rapid decline in serum bilirubin levels and relief of pruritus is known to shorten the duration of prolonged cholestasis and improve platelet number.



**Figure 1: Bone marrow features of aplastic anemia and excess fatty tissue**

Hepatitis-associated aplastic anemia (HAA) was first described in two patients in 1955 by Lorenz and Quaiser. HAA has been defined as a variant of aplastic anemia, which occurs either concurrently with or within 6 months of infection associated with an increase in the level of serum alanine aminotransferase to at least five times the upper limit of the reference range;<sup>[4-7]</sup> it most often develops in adolescent boys and young men, who present with severe pancytopenia 2–3 months after an episode of acute hepatitis. The marrow failure may be rapid and severe; it is usually fatal if untreated.

Limited number of aplastic anemia cases have been reported in association with HAV, hepatitis B, and hepatitis G; parvovirus B19; Epstein–Barr virus; transfusion-transmitted virus; and echovirus.<sup>[8,9]</sup> HAA is a rare complication of HAV. The first case of aplastic anemia associated with HAV infection was reported by Smith *et al.* in 1978. The majority of the reported cases have blood group A; patients with blood group O have also been reported. In a Swedish study on children with severe hepatitis who developed aplastic anemia, four out of six patients had blood group A and two had blood group O.<sup>[10]</sup> Three cases reported from Syria were young male with blood group A Rh positive.<sup>[11]</sup> Our patient was a young male with blood group O Rh positive who developed aplastic anemia post fulminant HAV infection.

The mechanisms of aplastic anemia after an episode of hepatitis are still unknown. Earlier theories suggested that liver failure causes the accumulation of a substance that has a toxic effect on the bone marrow. Our patient denied any history of traditional herbal treatment, but on examination of the skin, we noticed several cautery marks.

HAA has also been described with a very low CD4/CD8 ratio and an increased percentage of HLA-DR<sup>+</sup> CD8 cells.<sup>[7]</sup> These observations suggest that marrow failure in HAA is mediated by CD8 T cells.<sup>[5]</sup> The marrow aplasia is mediated by immunological mediators possibly by gamma interferon or cytokine cascade; immunosuppressive therapy has been shown to have 70% response rate.<sup>[12]</sup> With bone marrow transplantation, 82% of patients survive beyond 5 years; our patient is on immunosuppressive medications and listed for urgent bone marrow transplant. The most important factors predicting worse prognoses include patients over 20 years and a long period between diagnosis and initiation of treatment.<sup>[13]</sup> The most common causes of death are bleeding and infection; however, spontaneous resolution has been reported.<sup>[10]</sup>

## CONCLUSIONS

Prolonged cholestasis followed by aplastic anemia is a very rare complication of HAV, precipitated by hematological, genetic, and/or immunological abnormalities. Early diagnosis, prompt investigations, and proper treatment are essential for survival.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient's guardian has given his consent for his child's clinical information to be reported in the journal. The patient's guardian understands that his child's name and initials will not be published, and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

## Authors' contributions

All authors contributed to the care of the patient, drafting of the report, revision, and approval of the final version.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

## Compliance with ethical principles

No prior ethical approval is usually required for single case reports. However, the parents of the patient provided consent for publication of the case.

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