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HEPATITIS A-TRIGGERED SEVERE HEMOLYTIC ANEMIA IN AN UNDIAGNOSED G6PD DEFICIENCY PATIENT

General Medicine

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ABSTRACT

Hepatitis A, the most widely recognized form of viral hepatitis, typically presents as an asymptomatic and self-limiting illness. However, in individuals with G6PD deficiency, the symptoms can resemble those of fulminant hepatitis. In this case report, we describe a patient with previously undiagnosed G6PD deficiency who contracted hepatitis A. Within 48 to 72 hours of admission, the patient developed severe hemolytic anemia and both direct and indirect hyperbilirubinemia. The patient received symptomatic treatment, and their blood parameters returned to normal within three months of the illness. Swift and accurate diagnosis and evaluation of these patients are imperative to prevent complications.

KEYWORDS

Hepatitis A, Hemolytic anemia, G6PD deficiency, Vitamin K

INTRODUCTION

G6PD deficiency, an X-linked disorder, stands as one of the most prevalent enzyme deficiencies on a global scale. While often asymptomatic, red blood cells with this deficiency can experience hemolysis when confronted with specific dietary items, medications, or infections. In such instances, these cells struggle to manage the surplus of oxygen-derived free radicals, leading to pronounced hemolysis and elevated bilirubin levels. In this discussion, we delve into the probable precipitating factors which led to severe hemolytic anemia and hyperbilirubinemia in a patient with acute viral hepatitis.

Case Report

A 37-year-old previously healthy male presented with a range of symptoms including high-grade fever, vomiting, abdominal pain, yellow discoloration of eyes, and dark urine over the past week. He reported recent travel and consumption of food and water outside of his usual routine a week before the onset of these symptoms. There was no history of decreased urine output, dyspnoea, pedal edema, or lymphadenopathy. He denied any history of alternate medicine use, NSAIDs, or alcohol consumption. There was no family history of liver disease, and his vital signs were stable. On physical exam, he had scleral icterus and mild right upper quadrant abdominal pain without guarding or rigidity. He was alert and oriented without focal deficit or asterixis. He had no ascites. Vital signs were within normal limits. Laboratory findings included urine routine suggestive of 1+ protein, +++ bilirubin, 4-5 white blood cells, and no casts, PT/INR-11.6/1.02, serum creatinine1.02mg/dl, BUN-10.7 mg/dl, serum ammonia-33.3umol/l. Tests for dengue, malaria, covid-19, and influenza were negative. A viral hepatitis workup indicated hepatitis A virus with positive IgG and IgM. Abdominal and pelvic ultrasound showed mild ascites. Symptomatic management and hydration were initiated, and vitamin K injections were administered due to worsening liver function tests. In the next 48 hours, there was a significant drop in haemoglobin levels, prompting an investigation for haemolytic anaemia. Laboratory results, including a peripheral smear, suggested macrocytic polychromatic cells and fragmented RBC, reticulocyte count of 5.6%, LDH at 1112U/L, haptoglobin below 10 mg/dl, negative occult blood in stool, normal active B12 and iron studies, and a negative Coombs test.

Additional tests included ANA at a 1:100 titre with a mid-body pattern, C3 at 116 mg/dl, and C4 at 25.7 mg/dl. RBC membrane studies were negative. Qualitative and quantitative deficiency of G6PD was identified with a value of 1.47 units/gm of HB. The patient was managed with minimal medications, and the decision to defer blood transfusion was made. Gradual improvement in both symptoms and laboratory values was noted. Two months later, upon recovery, the results of ANA tests were negative, and his haemoglobin level had returned to normal.

	Day 0	Day5	Day 9	Day 11	Day 15	Day 25	Day 35	Day 45	Day 65
Hemoglobin (g/dl)	13.6	8	7.3	7.4	8.2	9.6	11.8	13.4	14.2
Bilirubin (total) (mg/dl)	7.68	49.3	43	31.10	23.30	12.21	6.35	2.72	1.02
Bilirubin (direct) (mg/dl)	3.23	45	40	30.60	22.6	11.34	5.50	2.26	0.68
Aspartate transaminase (U/L)	4806	391	229	204	189	189	72.1	56.1	27.8
Alanine transaminase (U/L)	3449	1117	767	610	502	347	151.3	90.5	57.9
Alfa-fetoprotein (ng/ml)	9.5	10.64	12.2	24	28	26.8	25.1		
LDH (U/L)	750	1117	1550	1100	800	546	333		

Table 1: Graphical Presentation Of Blood Parameters

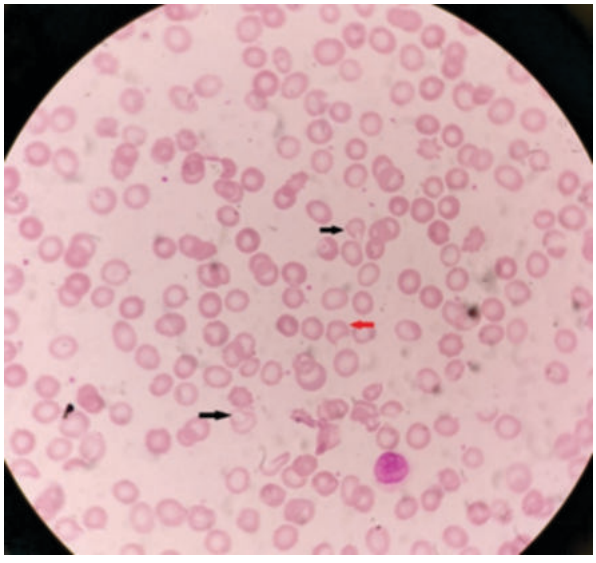

Figure 1: Red Arrow: Bite Cells ; Black Arrow: Blister Cells

DISCUSSION

According to a report from the World Health Organization, about 7.5% of the world's population carry one or two genes for G6PD deficiency, the proportion ranging from a maximum of 35% in parts of Africa, to 0.1% in Japan and parts of Europe and about 9% of the world population are genetically G6PD-deficient(1). While in India Devendra et al. 2020 reported that the prevalence rate of G6PD deficiency varied between 0.8 and 6.3% with an overall prevalence of 1.9%. This prevalence is population-specific and tends to be higher among tribal communities it is more prevalent in the northern states of India compared to other regions.(2)

The typical progression of hepatitis A infection is generally thought to be self-limiting. Nonetheless, it can result in a spectrum of outcomes, ranging from asymptomatic cases to potentially fatal fulminant hepatitis. Furthermore, mild to moderate anaemia is occasionally observed, potentially originating from an autoimmune mechanism. A retrospective study done by Chau et al. 1997 On 434 patients found that 4% of patients with acute viral hepatitis had acute haemolysis, and 53% of those had G6PD deficiency(3). Whether the cause of haemolytic anaemia is solely due to G6PD deficiency or autoimmune factors is a question to consider. Berlin and colleagues reported that in individuals without autoimmune conditions who have various infections, there can be elevated levels of autoantibodies. These autoantibodies may arise due to molecular mimicry of microbial peptides that resemble self-tissues. The temporary presence of autoantibodies in our patients might be explained by this phenomenon (4,5).

In individuals with G6PD deficiency, the enzyme is deficient both in liver cells and erythrocytes. This deficiency has been proposed as a factor that could impede the repair of hepatocytes damaged by viral hepatitis. Consequently, due to the heightened oxidative damage to hepatocytes resulting from glutathione depletion, it may exacerbate liver damage. Therefore, in addition to experiencing increased haemolysis, these patients are more likely to develop hyper-bilirubinemia. Based on a retrospective analysis done by Jain et al. in India in the year 2013, of 20 patients of hepatitis A with G6PD deficiency, he found that patients with G6PD deficiency had significantly higher peak bilirubin levels, peak creatinine levels, prothrombin time, and hospital stay. Haemolysis was also more severe in the study group (6).

The triggering factor for severe hemolysis in our patient, who had previously remained undiagnosed with G6PD deficiency, remains unknown. The two potential causes we considered were the infection and the administration of vitamin K. Similar findings were noted by Ozbay Hosnut et al. in 2008, where two children with hepatitis A infection developed hemolytic anemia, alongside significantly abnormal liver and renal function tests, anemia, leucocytosis, and hyperbilirubinemia. Both patients had G6PD deficiency and autoimmune antibodies. They were administered vitamin K upon admission, potentially contributing to a sudden decline in hemoglobin levels(7). Numerous authoritative internal medicine textbooks, like Harrison's Principles of Internal Medicine, Oxford Textbook of Medicine, and Cecil Textbook of Medicine, have suggested vitamin K as a possible hemolysis trigger in G6PD-deficient individuals. However, a study by Kaplan et al. found that G6PD-deficient red blood cells are not significantly prone to oxidative damage from vitamin K1(8). Consequently, the decision to administer vitamin K should be determined by the treating physician based on individual patient circumstances.

Additionally, cases of acute renal failure leading to hemodialysis secondary to severe intravascular hemolysis in Hepatitis A with preexisting G6PD deficiency have also been reported.

The primary approach to treatment revolves around avoiding medications that could trigger haemolysis and closely monitoring the patient's condition. The use of steroids in treatment is a subject of consideration. The precise role of plasmapheresis in managing autoimmune haemolytic anaemia(9) and extra corporeal therapy in renal failure still lacks clarity (10).

While hepatitis A vaccination is not currently recommended for routine use, Chau et al. in 1997 recommended its use in high-risk individuals, especially those with G6PD deficiency (3).

CONCLUSION

We recommend a vigilant monitoring approach for patients presenting with acute viral hepatitis A and significant hyperbilirubinemia to detect and address potential haemolysis and hyperbilirubinemia. In cases of acute hepatitis A coupled with severe haemolysis, it is essential to consider G6PD deficiency as part of the diagnostic process. While the use of vitamin K in patients with abnormal liver function tests is not unusual, it is advisable to exercise caution, especially in these patients, due to its potential to worsen hemolysis, until G6PD deficiency is ruled out. Additionally, we advocate for the evaluation of G6PD-deficient individuals for hepatitis A vaccination and emphasize the importance of genetic screening for the G6PD phenotype. This proactive approach is particularly crucial for high-risk ethnic populations, with the aim of preventing haemolytic episodes among G6PD-deficient patients.

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