

NON-AUTOIMMUNE HEMOLYTIC ANEMIA –A RARE COMPLICATION OF ACUTE HEPATITIS B INFECTIONMegha K. Mukundan¹, Sukdev Manna², Minakshi Dhar*³ and Rohit Gupta⁴¹Junior Resident, Department of General Medicine.²Senior Resident, Department of Clinical Immunology & Rheumatology.³Additional Professor & Head of The Department, Department of General Medicine.⁴Associate Professor, Department of Gastroenterology All India Institute of Medical Sciences, Rishikesh, Rishikesh, Uttarakhand, 249203, India.***Corresponding Author: Dr. Minakshi Dhar**

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ABSTRACT

Hepatitis B infection is quite common infection in this part of North India. The clinical presentation and complications of acute hepatitis B are related to onset and extent of liver failure. Here we report a very rare complication of acute hepatitis B in 61-year-old male patient. He was admitted with features of acute hepatic failure with grade 1 encephalopathy and coagulopathy. Patient was started on Tab Tenofovir 300 mg/day along with supportive and symptomatic treatment. Patient was improving clinically and laboratory parameters also showed improving trend. On day 8 of admission patient had a syncopal attack. Investigations revealed significant drop in haemoglobin level from 15.8 gm/dl to 5.8 gm/dl. Liver function showed improvement except increase in serum bilirubin. Other investigations revealed high LDH, haemoglobinuria, low haptoglobin with peripheral blood smear suggestive of acute haemolysis. Direct Coomb's test was negative. G6PD values were normal limits. Diagnosis of non-haemolytic anaemia secondary to acute hepatitis B infection was made. Patient was transfused 8 units of packed red blood cells in between in view of low haemoglobin. He was started on oral steroids in view of rapid fall in haemoglobin level despite blood transfusion. Haemoglobin improved over two weeks to 10.7 mg/dl. He is doing well with steady rise in haemoglobin level even after stopping of steroid after gradual tapering over a period of 1 month. According to previously published data acute viral hepatitis especially A, B, E mono or co-infection decreases lifespan of RBCs, but rarely results in severe life threatening haemolytic anaemia and that too in absence of pre-existing blood cell and liver pathology.

KEYWORDS: Acute hepatitis B, Haemoglobinuria, G6PD, Haemolytic anaemia.**INTRODUCTION**

Acute viral hepatitis is a common disease that we observe and manage in OPD or IPD basis. Viral hepatitis can cause mild haemolytic anaemia during acute phase but severe haemolytic anaemia associated with viral hepatitis in the absence of intrinsic red cell defect or pre-existing liver pathology is a less common entity and there are very few cases reported in literature from all over the world.^[1,2] We report a case of coombs negative severe haemolytic anaemia associated with acute hepatitis B infection during recovery phase. We assume that some acquired immunological phenomenon other than known autoimmunity caused haemolytic crisis in our patient as he improved with steroid therapy.

CASE

A 61-year-old male was admitted in AIIMS Rishikesh with fever, jaundice and generalised tiredness for 1

month. Patient was apparently normal 1 month back when he developed moderate to high grade fever with chills associated with gradually progressive jaundice and generalised tiredness. Fever subsided within 1 week but the jaundice progressed with deep yellowish discoloration of sclera, skin and patient had dark coloured urine for 1 week. He had altered sleep rhythm for the same duration. He is a retired teacher by profession with no major comorbidities or blood transfusion, and takes mixed diet. On physical examination he was deeply jaundiced with palpable liver of 5 cm below the right costal margin with no splenomegaly. Vitals were stable with a pulse rate of 88/minute, Blood pressure of 110/70 mmHg, respiratory rate of 14/minute. We made provisional diagnosis of acute viral hepatitis with grade 1 hepatic encephalopathy and initiated treatment in that line.

Routine investigations were done and his serum serology was positive for HBs Ag and anti IgM HBc.

Table 1: Baseline investigations (23/06/2018).

Haemoglobin(13-17 g/dl)	15.3
TLC(/cumm)	4200
DLC	N48L33M13
PLATELETS(/cumm)	2.3L
SGOT(0-50 U/L)	397
SGPT(0-50 U/L)	315
TB/DB(0.3-1.2 mg/dl)/ (0.00-0.20 mg/dl)	39.4/26
PT/INR	34.7 /3.19
USG ABDOMEN	hepatomegaly of 16.8 cm with mild ascites and thickened gall bladder wall with minimal pericholecystitis
HBsAg	REACTIVE
Anti HBc IgM(<0.1)	9.16
Hep A, C,E, HIV SEROLOGY	NON-REACTIVE

His baseline lab report was suggestive of acute severe hepatitis B infection. So Tenofovir 300 mg once daily with other supportive treatment for hepatic encephalopathy i.e lactulose, ursodeoxycholate acid, rifaximin, vitamin K, intravenous fluids and PPI's were started according to standard guidelines. Patient became better symptomatically over next 5-6 days and LFT showed an improving trend.

On day 8 of admission patient developed fever spikes of 101°F with macular eruptions mainly in the upper extremities. Patient had one episode syncopal attack. Repeat history taking did not reveal any feature suggestive of central nervous system, cardiovascular disease or acute blood loss. On examination, he had severe pallor with significant orthostatic hypotension. On

repeat investigation (table 2), we found significant drop of his haemoglobin level. Dermatology opinion was sought for evaluation of skin lesions and they made a diagnosis of papular urticaria. Workup for anaemia and fever was done (table 3). 8 PRBCs were transfused in the subsequent days as he had symptomatic severe anaemia and there was steady fall in haemoglobin in between transfusions. Based on results of repeat investigations we made a provisional diagnosis of acute haemolytic anaemia. Patient had high LDH, haemoglobinuria, decreased haptoglobin level with peripheral blood smear suggestive of hemolysis. But coombs test came out to be negative and G-6PD level was within normal limit. Patient was being adequately hydrated to prevent pigment nephropathy.

Table 2: serial laboratory investigations.

Date	27/06	29/06	01/07	05/07	07/07	10/07	11/07	09/08
Hb(13-17 g/dl)	11.3	10.9	5.1	5.4	6.5	7.5	8.6	10.7
TLC(/cumm)	6600	6500	8862	9168	12800	18790	20200	9800
DLC	N68L23	N70L19	N78L14	N80L13	N76L12	N81L8	N83L7	N75L14
PL(L/cumm)	2.17	2.3	2.5	2.32	2.96	2.88	2.53	2.1
SGOT(0-50 U/L)	246	212	140	126		155		88.3
SGPT(0-50 U/L)	162	145	99	76		80		76
TB/DB(0.3-1.2/(0.00-0.20 mg/dl)	9.6/5.3	7.5/4.2	14.3/5.1	13.6/6.7		12.9/4.4		7.35/4.8
INR	1.71	1.1	1.05	1.07				
Cr/urea	0.60/39			0.76/28		0.69/31		
LDH(<248U/L)			2770	1870				

Table 3: work up for severe acute anaemia.

Peripheral blood smear	Numerous schistocytes, polychromasia s/o haemolysis, NEGATIVE for malarial parasites
G6PD	N
ICT, DCT	NEGATIVE
URINE FOR FREE Hb	NEGATIVE
Haptoglobin(mg/dl)	<30
Dengue, malaria, scrub typhus serology	NEGATIVE

Stool for occult blood

NEGATIVE

As other causes of haemolysis were ruled out, a diagnosis of coomb negative haemolytic anaemia due to an inflammatory process probably due to recovery of underlying hepatitis was made. After reviewing literature, we started Prednisolone at a dose of 0.5 mg/kg/day. Patient symptomatically improved with the treatment on the subsequent days. His laboratory parameters also showed improving haemoglobin level. As patient was showing steady haemoglobin level and hemodynamic stability he was planned for discharge. At the time of discharge, his Haemoglobin levels were 8.6 g/dl, and total bilirubin: direct bilirubin was 12.9:4.45 mg/dl. He was followed up on OPD basis; steroid was gradually tapered off and stopped over 1month. There was no further fall in haemoglobin and the patient is doing well till date.

DISCUSSION

In the WHO South-East Asia Region an estimated prevalence of hepatitis B virus infection is 2.0% of the general population.^[3] Presentation of HBV infection can range from asymptomatic infection (most common) to chronic, acute or rarely fulminant hepatitis⁽⁴⁾. Acute hepatitis B is characterised by self-limiting acute inflammatory state with hepatocellular damage resulting in case fatality rate of 0.5–1%.^[4]

Acute viral hepatitis can present with subclinical haemolysis in 25 to 50 percent of patients.^[5] can also lead to shortening of life span of circulating RBCs. Pre-existing glucose-6-phosphate dehydrogenase deficiency, beta thalassemia and congenital nonspherocytic anaemia can complicate acute viral hepatitis precipitating acute haemolytic crisis.^[2,6-8] but very rare to happen without these defects in a patient with previously normal liver.

The purpose of this article is to describe the clinical course and management of a patient with coombs negative haemolytic anaemia complicating Hep B related acute viral hepatitis. Our patient had intravascular haemolysis. Exact aetiology of this haemolytic crisis is not known till date, mostly occurs during recovery phase as happened in our case, affects homologous and autologous cells to the same extent (probably extra corpuscular defect), lasting for months to years. Proposed etiological hypothesis in different studies are circulating antibodies, direct effect of virus on the cells, oxidative damage due to defective metabolism, some yet to be identified immune mechanism.^[9]

Lysis of transfused RBCs can temporarily complicate the clinical scenario causing pigment nephropathy due to haemoglobinuria so transfusion is usually withheld until indicated strongly. Our patient received multiple packed RBCs transfusion as he was symptomatic with severe anaemia and fortunately did not develop renal dysfunction.

Our patient had febrile episode and urticarial skin lesions before haemolytic crisis suggesting it to be an inflammatory process. Steroid was used empirically for such patients in various studies with assumed positive results.^[2,8,10] Based on these results we also used prednisolone and outcome was also favourable. We were able to stop steroid after one month suggesting it to be a transient phenomenon. Although we managed the patient successfully we could not delineate exact pathophysiology of that event. More studies are needed in this regard.

Learning points

- Patients with acute viral hepatitis should be followed up closely during recovery phase as haemolytic crisis can happen during this period.
- Proper supportive management like adequate hydration is to be ensured in patients with acute viral hepatitis to prevent renal complications.
- Short course steroids may be tried in acute viral hepatitis complicating as haemolytic anaemia.

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