CASE REPORT

Hepatitis B Leading to Megaloblastic Anemia and Catastrophic Peripheral Thrombocytopenia

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Abstract

Hepatitis B virus (HBV) typically causes chronic hepatitis, cirrhosis, and hepatocellular carcinoma. It is associated with a variety of extrahepatic complications. We herein, present a rare extrahepatic complication of HBV infection. A 32-year man presented with melena, bleeding from gums and fever. Peripheral blood examination revealed anemia, macrocytosis and severe thrombocytopenia. His hepatitis B surface antigen (HBsAg) was positive but deoxyribonucleic acid (HBV DNA) by polymerase chain reaction (PCR) was negative. Other hepatitis, human immune deficiency virus (HIV), dengue, and autoimmune serology were negative. Bone marrow examination revealed megaloblastic erythropoiesis. There was mild to moderate reduction of megakaryocytes in bone marrow, which was not compatible with severe peripheral thrombocytopenia. His response to cyanocobalamin and folic acid was remarkable for myeloid cell lines and moderate for erythroid cell lines, but poor to platelet counts. Platelet counts gradually improved to safe limits with eltrombopag, likely reflecting autoimmune pathogenesis for thrombocytopenia. This case report highlights multiple targets of HBV infection with associated multiple pathogenetic mechanisms.

Key Words: *Hepatitis B. Thrombocytopenia. Megaloblastic anemia.*

INTRODUCTION

Hepatitis B virus (HBV) is known to cause chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Extra-hepatic manifestations, commonly associated with hepatitis, are polyarteritis nodosa (PAN) involving small and medium-size vessels that can lead to significant morbidity and mortality, glomerulonephritis, palpable purpura and serum sickness like arthritis-dermatitis. These effects are believed to be autoimmune mediated.[1-3] Rare associations include autoimmune thrombocytopenia,[4] and myelosuppression,[5] and very rare association megaloblastic anemia along with coeliac disease.[6]

We herein, report a patient of hepatitis B having megaloblastic changes in the bone marrow myeloid and erythroid cell lines but mild suppression in megakaryocytes. Poor response of thrombocytopenia to treatment for megaloblastic anemia and erratic response with antiviral therapy and thrombocyte receptor agonists points to a peripheral pathology such as autoimmune causation.

CASE REPORT

A 32-year man was referred to us from a peripheral hospital with 4 months' history of jaundice, weakness and lethargy. One month back, he started having fever, melena, gum bleed and developed rash all over the body. There was no history of joint pains or any medicine intake. He had extramarital relations, but no history of drug addiction or alcohol abuse. On examination, he was pale, had very sick look, jaundice, ulcers on lips with obvious bleed in the posterior pharyngeal wall and purpuric rash all over the body (Figures 1 and 2). On abdominal examination, there was shifting dullness and palpable spleen. There were scattered crepitations on chest auscultation. Neurological, rheumatological and heart examination was normal. The investigations revealed hemoglobin, 3 g/dl. Total leukocyte counts (TLC) 4.3 x 10^9/l and platelet counts, 10 x 10^9/l. Mean corpuscular volume (MCV) was 100/L. Serum bilirubin was 126 mmol/l, alanine transaminase (ALT) 124 IU/L, and alkaline phosphatase (ALP) 238 mmol/l. His prothrombin time (PT) was 14 seconds and PTTK 34 seconds. Serum albumin was 3.8 g/dl. His hepatitis serology revealed HBsAg positivity. Hepatitis B e antigen (HBeAg), hepatitis e antibody (HBeAb), hepatitis B core antibody (HBcAb), hepatitis B virus deoxyribonucleic acid (HBV DNA) by polymerase chain reaction (PCR) were negative. Other serological studies including anti-hepatitis C virus (anti-HCV) antibodies, hepatitis D virus (HDV) antibodies, anti-human immunodeficiency virus (HIV), anti-hepatitis A virus (HAV), anti-hepatitis E virus (HEV), and dengue serology were negative. Autoimmune profile, i.e. anti-nuclear antibody (ANA), anti-smooth muscle antibody (ASMA), LKM and anti-mitochondrial antibody (AMA) were also negative. On upper gastrointestinal endoscopy, there were patches of sub-mucosal bleed in the gastric antrum (Figure 3). Abdominal ultrasound revealed normal liver

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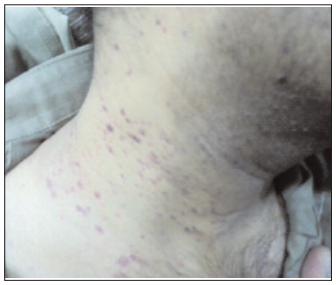

Figure 1: Purpuric skin rash.

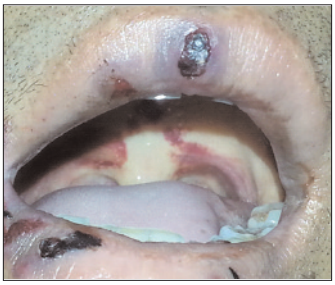

Figure 2: Bleed in posterior pharyngeal wall.

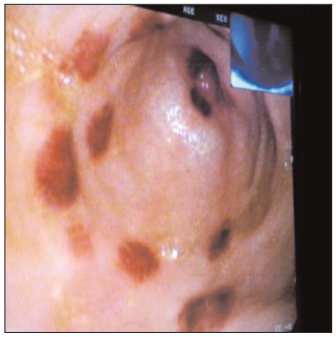

Figure 3: Sub mucosal bleed in gastric antrum.

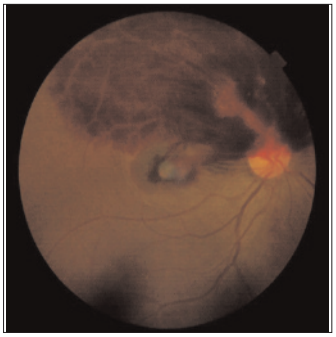

Figure 4: Bleed in retina of right eye.

and splenomegaly, the latter measuring 13 cm in length. He was given blood transfusion and platelet concentrates along with broad spectrum antibiotics. Keeping in mind hepatitis B infection, severe multiple site mucosal bleed, and rapidly deteriorating condition of the patient; he was started with oral tenofovir 300 mg/dl, despite undetectable HBV DNA levels but he did not show significant improvement. During hospital stay, he had reduced vision in right eye. On fundoscopy, there was a big patch of hemorrhage in right eye (Figure 4) and tiny hemorrhages in the left eye. Bone marrow examination revealed hyperplastic erythropoiesis with frank megaloblastic changes. Myelopoiesis was increased with increased metamyelocytes. There was mild to moderate reduction in megakaryocytes. His vitamin B12 level and serum folate levels were on the lower side. Anti-parietal cell antibodies and anti-platelet antibodies were negative. His tissue transglutaminase (tTG) IgM and IgG antibodies were done to rule out any associated coeliac disease, but were negative. He was started with intravenous cyanocobalamin 1000 mg, and oral folic acid 5 mg daily. He showed significant response in leukocyte count, which rose to 40 x 10^9/l. There was moderate response in hemoglobin, likely due to less bleed which became 8.6 g/dl with reticulocyte count of 21.4%. There was very mild response in platelet counts which only rose to 17 x 10^9/l, indicating some other pathological factor involved in severe peripheral thrombocytopenia. Eltrombopag, 25 mg twice daily, was started, which resulted in marked improvement in patient's condition. His bleeding stopped, rashes started disappearing and colour of the stool got better. Platelet counts rose to 47 X 10^9/l after 2 weeks of treatment with eltrombopag. After 10 days, leucocyte count was normalised and hemoglobin increased to 11 g/dl. He was advised to continue cyanocobalamin weekly and folic acid daily for next 4 weeks and then monthly thereafter. Further, he was given eltrombopag for another 2 weeks and tenofovir to be continued. At the end of one month, he was totally asymptomatic. Rash was settled. There was no active bleed and peripheral blood counts were within normal limits. After 6 months, there were persistent undetectable HBV DNA levels. His antiviral treatment was stopped because of unclear indications of the therapy. Thrombocytopenia persisted in the range of 45 x 10^9/L to 55x10^9/L, pointing to possible secondary autoimmune thrombocytopenia.

DISCUSSION

Hepatitis B virus (HBV) is a double stranded DNA virus which belongs to hepadnaviruses family. It has eight genotypes (A-H). Serological markers are HBsAg, HBeAg, HBeAb, Anti HBcAb (IgM and IgG) and hepatitis B viral DNA detection. The clinical manifestations of HBV infection vary in acute and chronic hepatitis. HBV associated hepatocyte injury is believed to be T-cell-mediated. Extrahepatic manifestations like PAN involving medium and small vessels, glomerulonephritis, serum sickness and palpable purpura are considered to be circulating immune complexes (CIC) mediated, present in 10 - 20% of patients with chronic hepatitis B. Controversial HBV associations are mixed essential cryoglobulinemia and popular acrodermatitis of childhood. HBV can cause myelosuppression,[5] but whether it can cause isolated suppression of a single cell line as in this case, needs further studies. Megaloblastic anemia along with celiac disease in association with HBV infection has been reported in case series but occurrence of megaloblastic anemia alone is a rare finding and needs to be evaluated with more studies. Thrombocytopenia, in association with HBV infection, is considered to be autoimmune-mediated. Despite endemicity of Hepatitis B in Southeast Asia and Africa, very few studies on associated thrombocytopenia have been reported.[7] In a study of 219 patients, thrombocytopenia was observed in 38 (17.7%) patients of chronic hepatitis B and 23 (10.6%) cases of inactive carriers.[8] Thrombocytopenia was either related to HBV infection despite inactivity or was autoimmune in etiology. Our patient showed a remarkable response with cyanocobalamin and folic acid in leukocyte cell lines with markedly increased leukocyte count, but moderate improvement in hemoglobin level, the latter possible due to associated continuous bleed. Response to platelet count was significantly poor with above mentioned treatments; however, platelet count improved to safe limits in 2 weeks after treatment with eltrombopag. This indicates

that the likely pathogenic mechanism of thrombocytopenia in this case was autoimmune. New oral, nonpeptide, thrombopoietin receptor agonist, i.e. eltrombopag is recommended in idiopathic thrombocytopenic purpura (ITP), drugs (interferon) and viral-induced thrombocytopenia as in patients with hepatitis C and on interferon based antiviral therapy.[9,10] In clinical trials, eltrombopag given for 6 weeks in chronic ITP, showed significant rise in platelet count as compared to placebo.[11] In this case, rise in platelet count after eltrombopag favours associated autoimmune phenomenon. This is a unique case having megaloblastic anemia, isolated megakaryocytic suppression and suspected autoimmune thrombocytopenia associated with HBV infection. This case report provides evidence that HBV infection can affect different targets in human body.

CONCLUSION

Many HBV associated extrahepatic complications are well established but some like selective cell line suppressions are still controversial and need more studies for further evaluation.

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