Case Report

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A Case of Acute Flare Leading to Hepatitis B Virus Reactivation Following Discontinuation of Nucleoside Analogues

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ABSTRACT

Background: Acute flares in chronic hepatitis B are mostly immunologic flares that often result from sudden withdrawal of the antiviral medications like Nucleoside Analogues. They can be life-threatening unless recognized and treated promptly, and there is increasing experience that preemptive antiviral treatment can diminish their occurrence and improve the clinical outcomes. The objective of this study is to report such a case, where sudden withdrawal of NAs led to Acute HBV Flare and HBV Reactivation in an Inactive HBV Carrier patient.

Case Presentation: This case report describes a 45 years old non diabetic normotensive woman presenting in the OPD of Brahmanbaria Medical College & Hospital 10 September 2022 with the complaints of yellow coloration of eyes and urine for 2 weeks and weakness, nausea, loss of appetite and low grade fever for the same duration. On examination, she was moderately icteric, had low grade fever, and there was mild tenderness in the right upper abdomen. On query, she stated that she was diagnosed as HBsAg positive four years back and after thorough evaluation, antivirals (NAs) were started. After continuing her medication regularly for the first three years, she stopped the drugs by herself, and came to us a few months later with her symptoms. She was diagnosed as a case of Acute HBV Flare leading to HBV Reactivation. Treatment was reinitiated, and she was counseled properly regarding not to stop medication by herself, and to be on regular follow up.

Conclusion: Acute HBV Flares and Hepatitis B Virus Reactivation are commonly found in patients who discontinue medication suddenly. Although most of the flares can be controlled effectively by prompt treatment, it is also not uncommon to find cases leading to hepatic failure, decompensation and death. So, all possible complications of treatment withdrawal patients should be monitored closely, and prompt treatment should be given.

KEY WORDS

Hepatitis B Virus; Flare; Reactivation; Nucleoside analogues discontinuation.

INTRODUCTION

Acute flares in chronic hepatitis B are common and may be caused by a number of identifiable and potentially treatable factors. There may be spontaneous reactivation of chronic hepatitis B or it may result from withdrawal of antiviral drugs. Flares can also result from using immunosuppressive medications like - cancer chemotherapy, antirejection drugs or corticosteroids; after antiviral therapy (Interferon and Nucleoside Analogues) HBV genotypic variation (Pre-core mutant, Core promoter mutant or HBV DNA polymerase mutant) or infections with other hepatotropic viruses (Hepatitis A, C or D virus and HIV).

The common reason for many of these exacerbation episodes is a change in the immunologic response to Hepatitis B Virus (HBV) and this may have no identifiable cause or be triggered by an increase in viral replication or genotypic change. Reactivation is frequently induced by medical treatment or treatment withdrawals. The immunologic flares that often result from sudden withdrawal of medications can be life-threatening unless recognized and treated promptly with antivirals. The experience with different nucleoside analogues used for the treatment of Hepatitis B virus mediated infection has increased our understanding of the molecular events behind hepatitis flares that occur when chronic hepatitis B is treated with drugs that potently inhibit HBV DNA polymerase.

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CASE PRESENTATION

A 45 years old non-diabetic, normotensive woman came on 10 September 2022 to the OPD of Brahmanbaria

Journal of Brahmanbaria Medical College
Volume 07 Issue 01 January 2025 ; 36-39

Medical College Hospital with the complaints of yellow coloration of eyes and urine for the last 2 weeks and weakness, nausea, loss of appetite with low grade fever for the same duration. According to her statement, she was apparently well before her symptoms arrived, then she noticed yellow coloration of her eyes and urine, which followed a prodrome like illness. She did not give any history of abdominal pain or distension of the abdomen, generalized itching, pale stool, vomiting, any nodular swelling in any part of her body, significant weight loss, or any history of taking herbal, homeopathic or ayurvedic medication over the last one year, She also complained of intermittent low grade fever, nausea, loss appetite and weakness. These were not associated with any cough, chest pain, alteration of bowel habit, dysuria, drenching night sweats or pruritus, previous TB or contact with any TB patients.

On query, she told that she was diagnosed as HBsAg positive about 4 years back, and vas evaluated thoroughly in BSMMU. After evaluation, antivirals were started, and she remained on regular follow up for the first 2.5 years, and continued medication. Her follow up investigations showed that HBV-DNA was undetected. So, after continuing antivirals for a further few months, she decided to discontinue her medication as per advice of a quack.After discontinuing medication for a few months, she developed her current symptoms, and came to us.

On examination, she was averagely built, moderately icteric, and had low grade fever (100^0F). Her BP was 100/70 mm of Hg, pulse was regular and 92/min, and the condition of her body skin was apparently normal. Examination of her abdomen revealed mild tenderness over the right hypochondriac region. Examination of all other systems were found normal.

We performed some investigations. The results were as follows :

CBC	Hb : 10.6 gm/dL, ESR : 28 mm in 1st hour, Total WBC Count : 8.80 x 10^9/L, Neutrophil 62%, Lymphocyte 30%, Platelet Count : 170 x 10^9/L
SGPT	289 U/L
SGOT	134 U/L
Bilirubin	7.7 mg/dL
Prothrombin Time	15 sec (INR : 1.25)
Alkaline Phosphatase	133 U/L
Albumin	34 gm/dL
Creatinine	0.8 mg/dL
Electrolytes	Na : 135 mmol/L, K : 4.1 mmol/L
HBeAg (ELISA)	Positive
Anti HBe Antibody (ELISA)	Negative
HBV DNA (PCR)	3.66 x 10^5IU/mL
AFP	333 ng/mL
Anti HCV (ELISA)	Negative
Anti HAV IgM	Negative
Anti HEV IgM USG of Whole Abdomen	Negative Liver normal in size having slightly coarse parenchyma. No splenomegaly. Biliary channels and Gall Bladder normal. No ascites. No lymphadenopathy.

She was diagnosed as a case of HBV Flare resulting in Reactivation of the virus. After her initial diagnosis four years back, she was put on Entecavir therapy (one tablet of 0.5 mg daily), which she discontinued after three years. So, we decided to start Tenofovir Alafenamide (One tablet of 25mg daily) along with some symptomatic medication. After thorough counseling and explanation of the disease, we advised her not to stop medication without consulting a specialist physician in future.

She was followed up weekly for the first one month, and by the end of four weeks, her Liver Function Tests became normal. After two months, USG and AFP were repeated, and found normal. After six months of continuous treatment, a complete and thorough checkup was performed and we found normal LFTs, AFP and USG, HBV DNA Undetected, HBeAg Negative and Endoscopy of Upper GIT was also normal. She is still on regular follow up, continuing her medication as advised and enjoying apparently good health.

DISCUSSION

The natural history of chronic hepatitis B is punctuated by spontaneous flares of the disease in which substantial elevation of serum aminotransferase levels occur. The acute exacerbative episodes are precipitated by reactivated infection, and it has been reported that low basal viremia increases markedly before an increase in serum aminotransferase level is appreciated.[1] In the past, these acute flares might have been mistaken for episodes of acute viral hepatitis.[2] The flares are potentially important clinically because they can have severe or even fatal consequences.[3,4] It is not uncommon to encounter episodes of abrupt elevation of Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) to 2 to 5 times previous levels. Less intense elevations are even more frequent if patients are monitored closely.[5]

Flares become more common during adulthood because of a breakdown of immunotolerance to HBV.[6] Some patients experience a number of symptoms such as

Journal of Brahmanbaria Medical College
Volume 07 Issue 01 January 2025 ; 36-39

fatigue, nausea and anorexia during an acute flare, but many patients, particularly those who have mild or early disease, remain asymptomatic.[7] Occasionally signs of frank liver failure will become obvious, particularly when this is superimposed on advanced chronic hepatitis B.[8]

Reactivation of HBV replication is a well-recognized complication in patients with chronic HBV infection who receive cytotoxic or immunosuppressive therapy.[9] Suppression of the normal immunological responses to HBV leads to enhanced viral replication and presumably results in widespread infection of hepatocytes.[10,11] On discontinuation of immunosuppressive medications immune competence is restored and infected hepatocytes are rapidly destroyed.[12] Theoretically, the more potent the immunosuppression, the greater the level of viral replication, and the greater the clinical consequences of sudden withdrawal.

Patients with cirrhosis are thought to have a higher risk of hepatic decompensation following a transaminase flare during a hepatitis B reactivation event, but in this case, there was no evidence of cirrhosis or portal hypertension (Although liver biopsy was not done) which suggests that all patients with hepatitis B may be at risk of this event on drug withdrawal.[13] Reported cases of transaminase flares following antiviral withdrawal occurred in patients with abnormal liver function tests and less so in those that had mild abnormalities in liver function.[2,14]

Many recent studies show that, antivirals can be safely withdrawnin those patients who develop HBeAg seroconversion during therapy.[15] In the setting of anti-hepatitis B e antigen positive chronic hepatitis B, the timing of cessation of nucleoside analogues and duration of therapy is uncertain. It is reported that among the individuals who stopped antivirals under controlled conditions and close monitoring, also developed hepatitis flares and incipient liver failure.[16] Physicians intending to treat patients with chronic hepatitis B using nucleoside analogues need to warn patients that stopping treatment may have serious consequences, particularly if patients have cirrhosis or remain HBeAg positive (Without seroconversion). Patients stopping therapy should be closely monitored for evidence of reactivation flares, and nucleoside analogues should be reinstituted before significant liver decompensation occurs.

LIMITATION

Liver biopsy was planned to see whether there is any evidence of cirrhosis or not, but could not be performed. Moreover, all investigations could not be performed due to financial constraints.

CONCLUSION

Acute flares are common in chronic hepatitis B and frequently follows after withdrawal of antiviral medication. These flares may lead to reactivation of the virus, and can be clinically serious when superimposed on established chronic viral hepatitis. To minimize the clinical impact of these acute flares, one requires an appreciation of high-risk clinical situations and prompt antiviral treatment when appropriate.

RECOMMENDATION

Regular follow-up of the patient should be advised and ensured according to schedule and all necessary investigations should be performed. Moreover, the patient should be warned never to stop medication by herself and consult with a specialist physician whenever there is any symptomatic deterioration.

DISCLOSURE

Both the authors declared no conflict of interest.

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Journal of Brahmanbaria Medical College
Volume 07 Issue 01 January 2025 ; 36-39

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