2. A Very Young Adult Female Patient with Hepatitis B Flare

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Submission date: 08-Dec-2023 04:59PM (UTC+0800)
Submission ID: 2252330622
File name: 2._A_Very_Young_Adult_Female_Patient_with_Hepatitis_B_Flare.pdf (1.96M)
Word count: 4443
Character count: 24182

A Very Young Adult Female Patient with Hepatitis B Flare: A Case Report

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ABSTRACT

Hepatitis B virus (HBV) infection is a major global health problem. It can cause chronic infection and put people at high risk of death from cirrhosis and liver cancer. This study aims to present a case of chronic hepatitis B flare in a very young adult patient. An 18-year-old previously healthy female presented with jaundice developing in one week, following the previous complaints of nausea, vomiting, abdominal pain, loss of appetite, and tiredness for about three months. The patient had no risk factors for getting HBV infection, but her HBsAg-positive mother was probably an inactive HBV carrier. The hepatitis B serological testing revealed HBsAg positivity, anti-HBs seronegativity, HBeAg positivity, anti-HBe seronegativity, anti-HBc IgM seronegativity, and high levels of HBV DNA detected > 1.70 × 10^8 IU/mL. There was a sharp increase in serum ALT to ≥ 5-fold ULN. The abdominal ultrasonography revealed a hepatitis feature, unremarkable portal venous flow and an extrahepatic biliary system. The liver transient elastography revealed 15.6 kPa of liver stiffness, which was in accordance with the F3-F4 fibrosis stage. These features were typical of a hepatitis B flare, the HBeAg-positive chronic hepatitis B, previously known as the immune reactive phase. A long-term nucleos(t)ide analog therapy was programmed with Tenofovir alafenamide 25 mg daily.

Keywords: *hepatitis B virus infection, chronic hepatitis b, immune reactive phase, flare.*

INTRODUCTION

WHO estimated that 296 million people were suffering from HBV infection in 2019, with 1.5 million new infections yearly. Eighteen million people are infected in the WHO South-East Asia Region, where 260 thousand incident cases in 2019.[1] Indonesia belongs to the top four countries, contributing to ≥ 80% of HBV infections worldwide in 2016. The prevalence of HBV infection in Indonesia is 7.1%, with 17.7 million total HBsAg positive infections.[2]

In highly endemic areas, including Indonesia, HBV is most commonly transmitted vertically from mother to child at birth from exposure to maternal blood and secretions at delivery.[3] The risk of developing a chronic HBV infection is directly related to the age at which one first becomes exposed to the HBV. Infections during infancy remain asymptomatic and carry a ≥ 90% chance of progressing to chronic hepatitis B (CHB).[4]

In daily practice, patients who have long been known to be HBsAg positive but asymptomatic suddenly develop severe symptoms similar to that of acute hepatitis. Patients with CHB still in the immune-clearance phase also often experience severe symptoms similar to acute hepatitis. To distinguish this stage from the reactivation phase that occurs in a previously inactive carrier state, this stage is called a

"flare." Reactivation and flare of CHB have received little attention from clinicians and are often diagnosed as acute hepatitis, although the incidence of reactivation and flare in CHB is relatively high. This condition is mainly caused by the natural history of chronic HBV infection that is not well understood and the limited access to laboratory facilities to detect these conditions, especially through quantitative HBV DNA testing. This study aims to present the detection and management of HBV flare in a very young adult patient.

CASE ILLUSTRATION

An 18-year-old female presented with a chief complaint of yellowish eyes developing in one week. At first, the patient had nausea, vomiting, abdominal pain, loss of appetite, and tiredness for about three months. Fever was denied. She was not on any over-the-counter medications but abdominal pain medications prescribed by a general physician. The complaints were worsening by her increased physical activities. The complaints were followed by cola-colored urine, yellowish eyes, and mild diarrhea, but neither black nor tarry stool. She did not have tattoos, drink alcohol, or use illicit drugs. She was not sexually active.

The patient was fully alert, and her vitals were stable (111/67 mm Hg blood pressure; an 85 bpm heart rate; a 19 breaths per minute respiratory rate; a 36.6°C axial temperature). She was in mild pain in the epigastrium (3 of 10 numeric rating scale). The BMI was 25.76 kg/m^2 (71 kg weight and 166 cm height).

There were no anaemic conjunctives, alopecia, skin rashes, or mouth ulcers. There was also no jugular venous distension, abdominal distension, caput medusa, or pedal edema. The liver was slightly tender upon palpation, and the spleen was not palpable. The remainder of the physical examination was unremarkable.

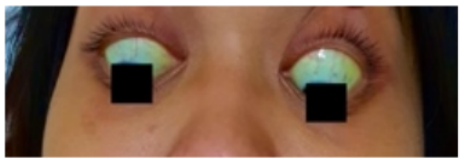

Figure 1. Inspection of the sclerae revealed jaundice.

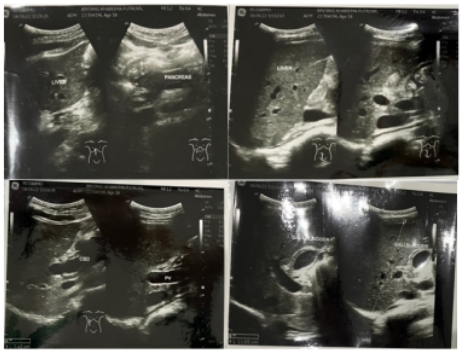

Figure 2. The abdominal ultrasonography revealed mild hepatomegaly with slightly decreased overall echotexture echogenicity. The portal venous flow, gall bladder, and extrahepatic bile ducts were unremarkable. The remainder of the abdominal ultrasonography was also unremarkable.

The patient underwent several initial laboratory examinations: AST 392.5 IU/L, ALT 491.3 IU/L, HBsAg positive, and anti-HAV IgM negative. One week later, the patient underwent further liver function tests: total protein 6.70 g/dL, albumin 3.72 g/dL, AP 138 IU/L, AST 590.2 IU/L, ALT 643.9 IU/L, direct bilirubin 2.76 mg/dL, and total bilirubin 4.26 mg/dL. Viral hepatitis serology tests revealed HBsAg positive, anti-HCV negative, and anti-HAV IgM negative. Anti-HIV was negative.

The patient was assessed with Chronic Hepatitis B flare or reactivation as the differential. The patient was admitted (7/6/2022) to improve her general condition while confirming the diagnosis with Hepatitis B serologic test (anti-HBs titer, HBeAg, and anti-HBc IgM) and quantitative real-time PCR assay for HBV DNA. The patient was treated supportively with i.v fluid Ringer acetate 500 mL/24h, Metoclopramide 5 mg/ 8h i.v, and nutritional supplementation. Ursodeoxycholic acid 250 mg three times daily was also prescribed. The nutritional intervention was arranged to high-calorie 2,100 kcal/day, high-protein 105 g/day, and a low-fat diet of 23 g/day.

The following day (8/6/2022), jaundice remained, but the patient felt better as her complaints of nausea, vomiting, and abdominal pain were reduced. The vitals were stable, and the

patient was pain-free. The Hepatitis B serologic test revealed: anti-HBs titer 2.65 IU/L, HBeAg positive, anti-HBe negative, anti-HBc IgM negative. HBV DNA RT-PCR detected > 1.70×10^8 IU/mL (> 8.23 log IU/mL). The diagnosis of chronic hepatitis B flare was established. Hence, the patient initiated an oral antiviral therapy with Tenofovir alafenamide (TAF) 25 mg once daily.

The following day (9/6/2022), the patient complained of nothing but jaundice. The liver function tests revealed improvement of the amino transaminases (AST 156.5 IU/L, ALT 288.3 IU/L), but the serum bilirubin levels remained elevated (direct bilirubin 3.58 mg/dL, total bilirubin 5.05 mg/dL). The medications were all well tolerated. The other laboratory examinations were unremarkable. The patient was discharged on 10/6/2022.

At outpatient evaluation (15/6/2022), the patient regained her health, and the jaundice was significantly reduced. The entire main family member underwent voluntary screening for HBV infection with the positive HBsAg results revealed. They were all not known to have been infected with HBV priorly. The evaluation of liver function tests showed better improvement in liver function tests (AST 143 IU/L, ALT 100 IU/L, direct bilirubin 3.58 mg/dL, and total bilirubin 3.98 mg/dL). Long-term oral antiviral therapy with TAF was continued.

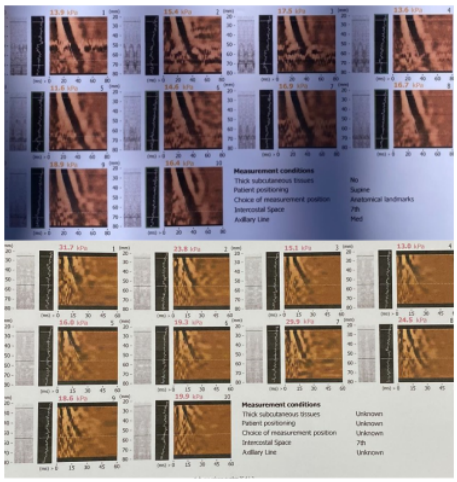

Figure 3. The transient elastography revealed 15.6 kPa of liver stiffness (upper figure) which was in accordance with the F3-F4 fibrosis stage and 19.6 kPa of spleen stiffness (lower figure).

DISCUSSION

In this case, the patient was a very young adult[5] 18-year-old female previously healthy. There was not any history of admission, tattoo, body piercing, ever having a blood transfusion, or using illicit drugs. The patient was also not sexually active. This case was a good model of perinatal transmission, which developed into a chronic infection. The patient had no risk factors for getting an HBV infection. However, her HBsAg-positive mother was probably an inactive HBV carrier. This presumptive risk factor was strengthened by the positivity of HBsAg in the entire central family. Perinatal transmission is the primary route of HBV transmission in many parts of the world, including Indonesia. The risk of developing a chronic infection is 90% following perinatal infection (up to 6 months of age).[4]

In acute resolving infections, the response of the innate and adaptive immune system to HBV is efficient and timely. Viral clearance involves the induction of a robust adaptive T cell reaction including both a cytolytic dependent and independent antiviral effect via the expression of antiviral cytokines, as well as the induction of B cells producing neutralizing antibodies preventing the spread of the virus. When the acute infection becomes chronic, there is a progressive impairment in HBV-specific T cell function. Consecutively, chronic HBV infection progresses through distinct disease phases.[6]

The signs and symptoms that belonged to the patient were presumptive for either acute or exacerbation hepatitis. The patient began to have constitutional symptoms for about three months, such as nausea, vomiting, abdominal pain, loss of appetite, and tiredness. The symptoms were worsening of her high physical activities in the case of preparation for the police officer entrance exam. Several weeks later, more specific liver disease symptoms emerged. The patient had jaundice and elevated serum amino transaminases (ALT 491.3 IU/L, AST 392.5 IU/L). Viral hepatitis serological testing revealed an HBV infection marked by HBsAg positivity, besides the anti-HCV and the anti-HAV IgM

seronegativities.

A history of acute or symptomatic hepatitis is often lacking in patients with chronic HBV infection. When symptoms are present, fatigue tends to predominate over other constitutional symptoms. Acute exacerbation of HBV infection may be associated with frank jaundice and signs of liver failure, particularly when superimposed on cirrhosis. During exacerbations of the disease, the clinical and laboratory picture is indistinguishable from that of acute hepatitis B. In other instances, patients may remain asymptomatic even during periods of reactivated hepatitis.[7]

Further investigation from the initial finding of HBsAg positivity revealed anti-HBs seronegativity, HBeAg positivity, anti-HBe seronegativity, anti-HBc IgM seronegativity, and high levels of HBV DNA detected (> 1.70×10^8 IU/mL). This hepatitis B serological condition was typically identified in the second phase of chronic HBV infection, the HBeAg-positive chronic hepatitis B, previously known as the immune reactive phase. The serum ALT levels were typically elevated (392.5 IU/L), indicating a liver injury.

The patient complained of yellowish eyes and tea-colored urine due to hyperbilirubinemia and bilirubinuria. The predominantly elevated serum direct bilirubin levels (direct bilirubin 2.76 mg/dL, total bilirubin 4.26 mg/dL) alongside the elevated alkaline phosphatase (138 IU/L) and aminotransferases (AST 590.2 IU/L, ALT 643.9 IU/L) were the features of intrahepatic cholestasis. Following the abdominal ultrasonography examination, these findings revealed no evidence of post-hepatic biliary obstruction.

The HBeAg positivity, in this case, was the key to determining the HBV infection phase. HBeAg is a viral protein found in serum early during acute HBV infection. HBeAg reactivity usually disappears at or soon after the peak in serum aminotransferase levels. The persistence of HBeAg for ≥ 3 months after the onset of illness indicates a high likelihood of transition to chronic HBV infection. The HBeAg finding in an HBsAg-positive patient's serum indicates a high level of viral replication and greater infectivity for intimate contacts. Near 90% of patients with HBeAg-positive CHB have been found to have serum HBV DNA levels persistently above 20,000 IU/mL.[8]

The anti-HBc IgM seronegativity in this case also supported the diagnosis of HBeAg-positive chronic hepatitis B, the second phase. During acute infection, anti-HBc is predominantly of the IgM class and is usually detectable for 4 to 6 months after an acute episode of hepatitis and rarely for up to 2 years. Anti-HBc of the IgM class may become detectable during exacerbations of chronic hepatitis B. Beside, anti-HBc of the IgG class is found in patients who recover from acute hepatitis B and those who progress to chronic infection.[7]

Chronic HBV infection is a dynamic process reflecting the interaction between HBV replication and the host immune response. Not all patients with chronic HBV infection have chronic hepatitis (CHB). The natural history of chronic HBV infection has been divided into five phases, taking into account the presence of HBeAg, HBV DNA levels, ALT values, and eventually the presence or absence of liver inflammation.[6] These consecutive phases are much more likely to be apparent in patients with the acquisition of CHB early in life through perinatal transmission.[9,10]

Most patients with mild-to-moderate chronic HBV infection are asymptomatic or have nonspecific symptoms such as fatigue. In general, the onset of jaundice can be caused either by a severe progressive disease with the development of decompensated cirrhosis or a flare due to immune reactivation. Elevated levels of bilirubin, alkaline phosphatase (AP), and gamma-glutamyl transferase (γGT) indicate intrahepatic cholestasis. In chronic HBeAg-positive hepatitis B, elevated aminotransferases and cholestasis may denote hepatitis flares in immunological reactivation, often followed by HBeAg seroconversion to anti-HBe and accompanied by a decrease in HBV DNA levels.[11]

APASL consensus described that one cause of severe flare that manifests as acute on chronic liver failure is a reactivation of hepatitis B. It is characterized by jaundice and coagulopathy, complicated within four weeks by ascites or encephalopathy in a patient with previously

diagnosed or undiagnosed chronic liver disease.[12] There are two kinds of flares occurred in chronic hepatitis B. The first one (HBeAg-positive) is exacerbation in the immune-clearance phase. The second one (HBeAg-negative) occurs after the inactive carrier phase or in the immune escape phase. It is essential to distinguish a "flare" in the second phase from a "reactivation" in the fourth phase.

The annual incidence of hepatitis B exacerbation was 27% in 358 HBeAg-positive patients and 10% in 279 HBeAg-negatives in a hospital-based study of CHB with a 2-year mean duration of follow-up.[13] There are many cases with multiple episodic hepatitis B flares in a single patient.[14–16] An immune flare is more commonly seen in the HBeAg-positive immune clearance phase (88.2–90.5%) than in the HBeAg-negative phase (23.8-50.0%) that occurs primarily due to spontaneous viral activation that indicates immune clearance activity.[17] Flares are an essential part of the natural history of hepatitis B because they can lead to histologic progression when they occur repeatedly and are moderate or severe.

An acute flare of hepatitis B may occur spontaneously during its natural course.[18] It presented as a sharp increase of serum ALT to ≥ 5-fold upper limit of normal (ULN) or ≥ 3-fold increase of the baseline level, whichever is higher. The high levels of serum HBV DNA trigger the host immune responses aiming to clear the virus.[19,20] Under this circumstance, active hepatocytolysis followed by hepatic decompensation may occur.[21]

Acute flares in CHB can occur spontaneously or in association with several circumstances. Superinfection by a non-HBV (such as HIV, HCV, or HDV) is one of the rare but critical contributing factors that cause acute flares of hepatitis B. In a patient with resolved or inactive HBV infection, an acute exacerbation or reactivation of hepatitis B occurs due to an increase in the replication of HBV. This reactivation process might occur spontaneously or after cancer chemotherapy and immunosuppressive treatment or due to alterations in the patient's immune function.[22]

In this case, the flare of hepatitis B was triggered by the high workload of physical activities in the case preparation for the police officer entrance exam. Although, it is not clear if severe physical or emotional stress can weaken the immune system and lead to a secondary increase in viral replication. In patients who acquire HBV infection early in life, flares become more common during adulthood. In this situation, the flares are almost certainly host-driven rather than virally mediated, and although poorly understood, they are most likely the result of a change in the regulation of viral antigen-specific T cells.[23]

To reduce overtreating of patients who may be at lower risk of developing significant liver disease, other markers of significant liver disease should be assessed before starting therapy. Approaches can include non-invasive markers of fibrosis such as transient or ultrasound elastography (FibroScan®, Echosens, Paris, France).[24] In this case, the patient had severe fibrosis (F3-F4) as transient liver elastography revealed 15.6 kPa of liver stiffness for the value of ALT 100 IU/L, which was elevated but < 5 × ULN.[25] The spleen stiffness was 25.9 kPa. Spleen stiffness correlates with liver fibrosis and helps determine the level of fibrosis in the METAVIR scoring system. In patients infected with HBV or HCV, spleen stiffness increases even when liver elasticity remains unaltered.[26]

Ringer acetate containing electrolyte and Metoclopramide as an antiemetic was administered supportively for nausea and vomiting. As lactate would be primarily metabolized in the liver,[27] we chose acetated over lactated Ringer for our patient with hepatic dysfunction. The anti-cholestatic effects of Ursodeoxycholic acid in intrahepatic cholestasis of CHB remain unclear, despite some evidence in intrahepatic cholestasis of pregnancy, liver disease of cystic fibrosis, progressive familial intrahepatic cholestasis, and chronic graft-versus-host disease.[28,29]

The patient was overweight (BMI 25.76 kg/m^2), receiving 30 kcal/kg/day, high-protein 1.5 g/kg/day, and a low-fat diet of 10% daily energy requirement. In cirrhotic patients, total energy expenditure (TEE) varies between 28–37.5 kcal/kg/day. Protein needs are based on the minimum protein intake required to maintain

nitrogen balance. In cirrhotic patients, protein intake recommendation is 1.2–1.5 g/kg/day to prevent loss of muscle mass and reverse muscle loss in those who are sarcopenic.[30] In cholestatic patients, a low-fat diet is recommended to manage fat malabsorption.[31]

This patient was treated with a nucleus(t)ide analog therapy. Tenofovir alafenamide (TAF) 25 mg once daily was prescribed. Nucleos(t)ide analogs have become the standard of care for the treatment of most patients with treatment-naïve and treatment-experienced CHB. As the first-line therapies, Tenofovir and Entecavir lack side effects and high efficacy. Approximately 70-95% of HBeAg-positive and HBeAg-negative patients will achieve undetectable HBV DNA during the first year of treatment with Tenofovir disoproxil fumarate (TDF).[32] Virologic responses progressively increase with a longer duration of therapy. The serum HBV DNA levels usually decline with adherence to treatment. Antiviral resistance is uncommon with TDF, TAF, and Entecavir. In fact, no antiviral-resistant mutation has been identified in patients on TDF after seven years of treatment.[33]

Tenofovir alafenamide (TAF), a novel prodrug of tenofovir, is given a lower dose (25 mg daily) than TDF but is delivered more efficiently into hepatocytes. TAF is superior to TDF in terms of renal safety as measured by serum creatinine and glomerular filtration rate and bone safety as shown by dual-energy x-ray absorptiometry scans. In patients taking TDF who were switched to TAF, not only was viral suppression maintained similarly, but also improvement in renal function and bone mineral density and higher rates of serum ALT normalization was observed within 6–12 months.[34] It is also safe to take TAF in the early pregnancy[35] whenever the patient becomes pregnant.

CONCLUSION

We reported a chronic hepatitis B flare case in a very young adult 18-year-old female. This case was a good model of perinatal transmission, which developed into a chronic infection. The hepatitis B serological testing revealed HBsAg positivity, anti-HBs seronegativity, HBeAg positivity, anti-HBe seronegativity, anti-HBc IgM seronegativity, and high levels of HBV DNA detected > 1.70×10^8 IU/mL. There was a sharp increase in serum ALT to ≥ 5-fold ULN. The transient liver elastography revealed 15.6 kPa of liver stiffness following the F3-F4 fibrosis stage. These features were typical of a hepatitis B flare, the HBeAg-positive chronic hepatitis B, previously known as the immune reactive phase. The natural history of chronic HBV infection should be well understood in each phase.

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2. A Very Young Adult Female Patient with Hepatitis B Flare

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PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6

PAGE 7