Case Report

Fulminant Hepatitis with Negative Viral Serological Markers: A Possible Case of Occult Hepatitis B Virus Infection

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Abstract

Infection with hepatitis B virus (HBV) shows variable clinical manifestations ranging from asymptomatic carrier state, acute, chronic, fulminant, and occult HBV infection (OBI). OBI is defined as the presence of HBV viral DNA in the liver (with or without detectable HBV DNA in serum) of hepatitis B surface antigen-negative individuals tested with the currently available assays. A cutoff of HBV DNA if present is expected to be <200 IU/ml. As high as 20% of individuals with OBI carriage evidenced by HBV DNA detection could be nonreactive for anti-hepatitis B core or any other serological evidence of exposure to HBV. With a reported prevalence of 5.4% among blood donors in Ile Ife, Nigeria, OBI is a risk factor for chronic liver disease and hepatocellular carcinoma. Given the sensitivity of our diagnostic tools in this environment, it is likely that most cases of OBI are going undiagnosed among many blood donors. We present a case of fulminant hepatitis with negative serological markers for viral hepatitis in a 25-year-old male.

Keywords: Elevated liver enzymes, fulminant hepatitis, jaundice, occult hepatitis B virus infection

Introduction

Hepatitis B virus (HBV) infection shows variable clinical manifestations ranging from asymptomatic carrier state, acute, chronic, fulminant, and occult HBV infection (OBI). It can progress from acute state to chronic and eventually to cirrhosis and hepatocellular carcinoma or remain largely undetectable by routine screening methods. However, these clinical manifestations may vary depending on their age at infection. Symptoms are lesser in under 5 years old (<10%) than in adults (30%–50%).[1] The first report of occult silent HBV infection dates back to about 30 years ago. It was reported in the context of blood transfusion which resulted in the transmission of HBV by a donor who was positive for anti-hepatitis B core (HBc) as the only marker of HBV infection.[2] The prevalence of OBI varies according to geographical region. However, it also depends largely on the specificity and sensitivity of the routine serological assays or nucleic acid testing. Hence, some persons positive for occult HBV may not show any serological evidence of the disease. This may make it difficult to diagnose OBI in Nigeria using currently available screening methods. OBI is a risk factor for chronic liver disease and hepatocellular carcinoma. The persistence of the virus in the liver for a long time may initiate a very mild but continuing necroinflammation which may progress even faster in the presence of other causes of liver damage to cirrhosis.

We report a case of fulminant hepatitis in a patient without any serological evidence of viral markers for hepatitis.

Case Report

A 25-year-old male student of Odukpani tribe in Cross River state, presented with a 3-week history of pain in the right upper abdomen, deep yellowness of the eyes, nausea, and deep amber-colored urine. There was a history of fever and no prior history of alcohol abuse. At the onset of symptoms, he was treated with oral drugs such as P-alaxin, artesunate, some antibiotics including metronidazole, and multivitamins,

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but the jaundice persisted and even increased. The following results were obtained [Table 1]:

- Hepatitis B surface antigen (HBsAg) (rapid) Negative
- Hepatitis A virus (rapid) Negative
- Hepatitis C virus (HCV [rapid]) Negative
- Hepatitis E virus (enzyme-linked immunosorbent assay) Negative
- Human immunodeficiency virus (rapid) Negative

Abdominal ultrasound scan revealed a liver with span of 14 cm with increase in the periductal/perivascular echo. No focal lesion or ductal dilatation [Figure 1] gallbladder was contracted (patient had eaten 5 h before scan). There were no masses or stones. Other organs were normal. There was no ascites, bowel dilatation, or abdominal masses.

Chest X-ray was normal. He was managed as a case of acute fulminant hepatitis.

After 3 weeks on the above medications (antimalarial and antibiotics), jaundice persisted and the patient did not get any better.

Repeat laboratory investigations in a different laboratory were very comparable to what was obtained 3 weeks earlier at onset. Results of additional investigations done at the same time are contained in Table 2.

The results of HBV serological markers were as follows:

- HBsAg Negative
- HBsAb Negative
- HBeAg Negative
- HBeAb Negative
- HBcAb Negative

Urinalysis

Urine colour was deep amber and was turbid in appearance. pH=5.0, bilirubin = 3+, urobilinogen = normal. Other parameters were negative.

A complete blood count (CBC) and differentials showed a packed cell volume (PCV) = 42%, Total white blood cell (WBC) count = 4000 × 10^9/L, Differential WBC: Neutrophils = 72%, Lymphocytes = 22%, Eosinophils = 6%, Basophils = 0%. Erythrocyte Sedimentation Rate (ESR) = 43 mm/hr (Westergren method).

Table 1: Liver function test carried out at presentation

Test	Results	Reference interval
SGPT/ALT	281.0 U/L	0-40
SGOT/AST	185.0 U/L	0-40
Alkaline phosphatase	736.0 IU/L	80-290
Total bilirubin	210.33 umol/L	0-17.1
Direct bilirubin	138.68 umol/L	0-6.8
Indirect bilirubin	71.65 umol/L	0-10.26
Total protein	69.00 g/L	55.0-82.0
Albumin	41.00 g/L	37.0-53.0
Globulin	28.00 g/L	15.0-36.0
Gamma-glutamyltransferase	409.2 U/L	0.0-50.0

ALT: Alanine transaminase, SGPT: Serum glutamic-pyruvic transaminase, SGOT: Serum glutamic-oxaloacetic transaminase, AST: Aspartate aminotransferase

A diagnosis of HBsAg-negative acute HBV infection was made, and supportive treatment was commenced. The patient improved steadily while on treatment and was reviewed after 3 months. Clinical condition had improved significantly as evidenced by disappearance of jaundice, no abdominal pain, clear urine, and an optimal general well-being.

Repeat investigations showed normalization of liver function tests and other parameters.

The patient was followed up for 4 years, and there was no complaints of any symptoms suggestive of hepatitis. Further laboratory investigations were requested for including complete blood count, liver function test, HBV serological markers, HBV DNA, and HCV DNA. The results were all either normal or negative.

Discussion

Infection with HBV is divided into five clinical categories: asymptomatic, acute, chronic, fulminant, and OBI.[3] OBI was defined in 2008 during an international workshop in Italy as "presence of HBV viral DNA in the liver (with or without detectable HBV DNA in serum) of HBsAg-negative individuals tested with the currently available assays."[4] A cutoff of HBV DNA if present was expected to be <200 IU/ml. The infection is found in a significant number of chronic hepatitis due to HCV with hepatitis B viral DNA detectable in up to 30% of serum samples and 50% of liver biopsies.[5] Most frequently, OBI follows the resolution of acute hepatitis and continues indefinitely after clearance of HBsAg and biochemical improvement of liver function.[6] It has been suggested that up to 20% of individuals with occult HBV carriage evidenced by HBV DNA detection could be nonreactive for anti-HBc or any other serological evidence of exposure to HBV.[6] Our index client did not show any serological evidence of viral DNA either of HBV or HCV.

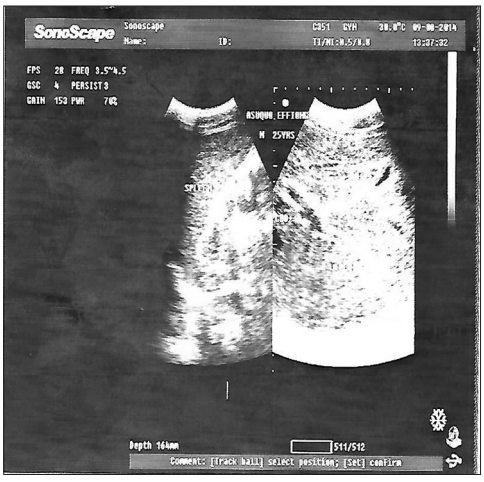

Figure 1: Liver ultrasound scan taken during fulminant hepatitis

Table 2: Additional investigations done 3 weeks after onset of symptoms

Test	Result (mmol/L)	Reference interval
Fasting plasma glucose	4.6	3.50-5.5
Total cholesterol	5.2	3.0-6.5
High-density lipoprotein cholesterol	1.2	0.9-1.5
LDL-C	3.1	2.5-3.8
TG	0.94	0.80-1.20
VLDL-C	0.19	0.40-0.60

TG: Triglyceride, LDL-C: Low-density lipoprotein cholesterol, VLDL-C: Very low-density lipoprotein cholesterol

HBV infection accounts for 500,000–1.2 million deaths each year making it the 10th leading cause of death globally.[7] Over 2 billion people worldwide show some serological evidence of past or current infection among which 350 million are chronic carriers.[7,8] Nigeria has a prevalence of 12.2% in the general population.[9] The prevalence of OBI among blood donors who tested negative for HBsAg but positive for anti-HBc using immunochromatographic methods was reported to be 5.4% in Ile Ife, Nigeria.[10] Their diagnosis was made based on finding a positive viral load in patients with a positive anti-HBc. Our index patient could have escaped detection if he was included in the study. However, that would not mean that he does not have OBI since the absence of HBV DNA in serum does not rule out the presence of OBI.[4] In general, the clinical course of viral hepatitis B infection is determined by the interaction of viral replication status and host immune response.[11]

Little or nothing is known about the course of HBV markers in the early phase of true OBI. It has been observed that despite a transient strong viral replication, a much less HBsAg can be demonstrated in the serum.[12] We were unable to carry out a viral load assay on our index patient during the acute phase due to financial constraints on the part of the patient. Perhaps, we would have been able to demonstrate some level of viremia at the time despite the likelihood of it being transient. Mutation at the level of transcription control regions of the polymerase domain may lead to decrease HBV replication and HBsAg expression. However, to increase sensitivity of detection, a novel immunoassay has been developed with potentials of detecting simultaneously HBV PreS1 and/or core-related antigens among HBsAg variants. The detection limits were determined to be 10 copies/mL for HBsAg-positive sera with different genotypes and 10 copies/mL for HBsAg variants containing sera[13] although the preferred lower limit of detection (LLOD) has been put at 5 IU/mL.[14] The LLOD of the methodology used for the HBV DNA assay in our index patient was 20 copies/mL. Given that patients with OBI have a lower viral load than their counterparts with overt infection, diagnosis will require the use of more sensitive methods to reduce the possibility of false-negative results. It has also been demonstrated that patients with long-standing abnormal liver function results of unknown etiology may have HCV RNA or HBV DNA in their peripheral blood mononuclear cells (PBMNCs) in the absence of anti-HCV antibodies, HBV markers, serum HBV DNA, and serum HCV RNA.[15] We did not examine the PBMNCs in our index patient to rule out this possibility.

There have been reported cases of transmission of HBV in blood transfusions to immunocompetent individuals by OBI carriers with anti-HBs.[11] However, such infections may be related to factors such as the amount of plasma transfused, viral load in the product, and immune factors affecting the susceptibility of the host to the infection.[16] A study conducted in India showed that a considerable number of HBV-infected donors remained undetected when HBsAg alone is used for screening.[17] This is the most frequently used method of screening in Nigeria presently. The implication is that many may have been infected with the virus due to the inadequate screening of blood before transfusion. One European study reported that 91% of 77 donor samples were HBV DNA positive/HBsAg negative. The viral load ranged from undetectable to 5640 IU/mL with a median of 25 IU/mL.[18] This shows that an undetected HBV DNA does not necessarily mean the absence of the infection.

In conclusion, OBI remains a major problem worldwide and poses an even greater threat in HBV endemic area like ours. Although liver biopsy was not done to enable testing for HBV DNA, this does not rule out the possibility of a positive OBI in the index patient. We, therefore, recommend that HBV screening should be carried out using anti-HBc as additional marker. If positive, a potential blood donor should be disqualified. There should be a high index of suspicion by all health-care givers, especially among persons with abnormal liver enzymes. This will go a long way to drastically reduce the infectivity rate by blood transfusion.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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