HEPATOCELLULAR CARCINOMA IN OCCULT HEPATITIS B VIRUS INFECTION: A CASE REPORT

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Occult hepatitis B virus infection is defined as the presence of hepatitis B virus DNA in the hepatocytes or serum of individuals who had tested negative for serum HBV surface antigen. Controversies remain as to the role of the occult HBV infection in the development of hepatocellular carcinoma (HCC) in immunocompetent individuals. It has been shown that the persistence of very low viral replicative activity during occult hepatitis B virus infection may induce mild liver necro-inflammation continuing for life, and substantial clinical evidence indicates that occult hepatitis B virus infection can accelerate the progression of liver disease towards cirrhosis that is considered the most important risk factor for hepatocellular carcinoma development. The aim of this case is to describe the clinical symptoms and laboratory data of the first case we encountered of HCC occurring in an OBI patient. A 52-year-old man came to the Infectious Diseases Unit because of right upper quadrant pain. Blood test showed negative for HBsAg, positivity for both anti-HBs and anti-HBc total, the quantitative assay of HBV DNA based on TaqMan technology was 2012 copies/mL, elevated serum alpha-fetoprotein level, the findings in abdominal ultrasonography and computed tomography showed a tumor in the right liver lobe with 12cm in size. The patient was transferred to the Military Hospital 175 Ho Chi Minh City for diagnosis of intermediate stage HCC, treated with transarterial chemoembolization (TACE) and antiviral treatment with tenofovir disoproxil fumarate (TDF).

Keywords: *Occult hepatitis B virus infection, hepatitis B virus, hepatocellular carcinoma, anti-HBc total.*

INTRODUCTION

According to the World Health Organization, chronic hepatitis remains a global health concern, especially in the Western Pacific region including Vietnam. In Vietnam, hepatitis B virus (HBV) prevalence is approximately 10%, and 40,000 people die each year from cirrhosis and liver cancer[1]. Hepatocellular carcinoma (HCC) is the sixth most commonly diagnosed cancer in the world (with 905,700 cases) and the fourth most common cause of cancer - related deaths (with 803,200 deaths)[2]. As HCC can be treated by surgical resection or liver transplantation if discovered early, prompt detection of early HCC is important. In Vietnam where HBV infection is endemic, there is extremely high incidence of HCC. The primary diagnostic approach for HBV infection is detecting the presence of serum hepatitis B virus surface antigen (HBsAg). Hence, regular HCC surveillance of patients with positive HBsAg is recommended. In some cases, currently available serum assays do not detect HBsAg, even though the HBV DNA is present in serum or liver tissue in low quantities. The latter is termed occult hepatitis B virus infection (OBI). The loss of HBsAg in the OBI population impedes the detection process and its clinical significance is controversial. No standard guidelines have been established for the management, in particular HCC surveillance, of patients following their sero-clearance of HBsAg, albeit low grade or intermittent presence of HBV DNA cannot be excluded in these patients.

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At the 2008 and 2018 Taormina expert meeting on OBI, OBI was defined as presence of HBV DNA in the hepatocytes in HBsAg negative individuals with or without detectable viral DNA in the serum by currently available assays. The intermittent viral load in the serum should be less than 200 IU/Ml3,4. OBI has been studied extensively for its clinical implications. First of all, from a public health point of view, OBI poses a potential risk for transmission though blood transfusion and liver transplantation, and in hemodialysis setting. There is evidence to support the proposition that, after transmission, the virus retains its ability to be reactivated, if the new host is immunocompromised. This makes OBI screening before transfusion or transplantation procedures a necessity in areas where HBV is endemic. In addition to the transmission, HBV persistence and its ability to integrate into host genome have sparked much interest in its potential role in the development of cancer5. However, the impact of OBI in the development of cancer in immunocompetent individuals has remained controversial.

The gold standard for defining OBI is liver biopsy for detection of HBV DNA in the liver, which may not have been readily available for all studies and for all patients. The sample size of most of the studies tend to be small and heterogeneous. As serum HBsAg are negative, it is challenging to identify and follow this group who had asymptomatic or subclinical HBV infection that has since resolved, without resorting to expensive nucleic acid testing.

The diagnosis of OBI is based on the sensitivity of assays used in the detection of HBV DNA and HBsAg. HBsAg assays with inadequate sensitivity or inability to detect HBV S variants may lead to a false negative HBsAg result and misdiagnosis of OBI in people with overt HBV infection. On the other hand, HBV DNA assays with inadequate sensitivity can result in false negative HBV DNA results and may lead to a missed diagnosis of OBI[4].

CASE DESCRIPTION

A 52-year-old man came to the attention of our Infectious Diseases Unit in 2021 because of right upper quadrant pain and mild fever for 4 days. On examination, he had abdominal tenderness without guarding and vitals were stable. Abnormal laboratory results were as follows: leukocyte count of 10,560 cells/mm3, platelet count of 347,000 cells/mm^3, alanine aminotransferase (ALT) level of 28.9 (3 - 30 IU/L), aspartate aminotransferase (AST) level of 26.3 (< 35 IU/L), creatinine level of 0.74 (0.6 - 1.3 mg/dL), glucose level of 5.23 (3.9 - 5.9 mmol/L), alpha-fetoprotein level of 51.4 (< 20 ng/mL), and negative for anti-HCV. The HBV serologies revealed the following: anti-HBc total and anti-HBs were both positive while his HBsAg was negative. The anti-HBs level was 16.07 mUI/mL.

The HBV viral polymerase chain reaction (PCR), which measures HBV DNA based on TaqMan technology, detected 2012 copies/mL.

The findings in abdominal ultrasonography showed a heterogeneous lesion with mixed echogenicity in the right liver lobe, moderately well-defined, thin hypoechoic peripheral zone (halo sign), 110x90 mm in size, bending sign (+) and thrombus in portal vein (Figure 1).

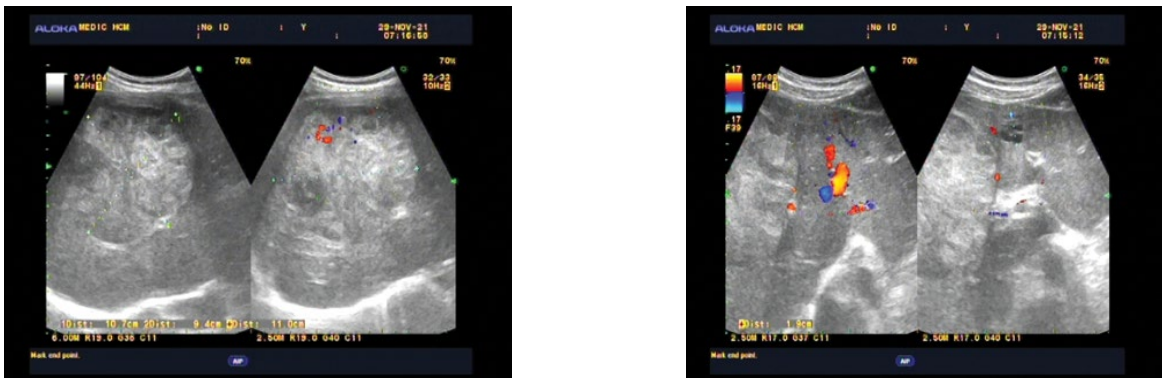

Figure 1. Conventional ultrasound showed a large lesion in the right liver lobe with and halo sign (thick arrow) and bending sign (thin arrow)

A triple-phase contrasted computed tomography (CT) of the liver was performed which highly suggested HCC. In CT, the inner diameter of the tumor was 12 cm. Edge-to-center filling and strengthening lesion, mild to moderate enhanced parenchyma at the arterial phase, and isodensity between the tumor parenchyma and the surrounding liver parenchyma at the portal vein phase or delayed phase (Figure 2).

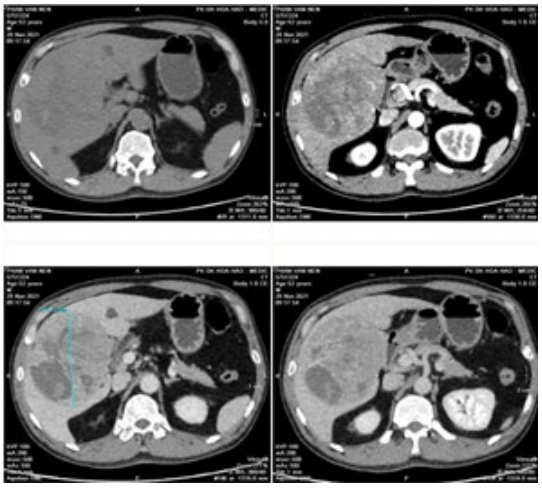

Figure 2. Computed tomography in the arterial phase shows hyper-enhancement. Computed tomography in the portal phase and delayed phase shows hypo-enhancement

He was transferred to the Military Hospital 175 Ho Chi Minh City with diagnosis of intermediate stage HCC. Two weeks after diagnosis, he received transarterial chemoembolization and started on tenofovir disoproxil fumarate. Additionally, 6 months after being started on antiviral therapy, a repeat PCR revealed undetectable HBV DNA. He is currently doing well and will continue to be monitored with periodic surveillance imaging at Military Hospital 175 Ho Chi Minh City.

DISCUSSIONS

Occult HBV infection not only has clinically diverse presentations, but also is associated with multiple complications: HBV reactivation, transmission of HBV, progression of liver disease, and HCC[4]. The case was representative of the complication with HCC.

Seropositive OBI cases are more prevalent than seronegative OBI. Seropositivity is defined as OBI with detectable anti-HBc with or without anti-HBs[6]. This occurs usually in the setting of a resolved previous HBV infection. These individuals either had an acute HBV infection or have CHB, and their previously detectable HBsAg became negative[3]. Conversely, seronegative OBI individuals may have either lost their antibodies over time or never had them from the start[3]. The patient was representative of seropositive OBI with anti-HBc total and anti-HBs were both positive, confirming prior exposure. His exposure history was unclear, but his case illustrates that screening using only HBsAg and anti-HBs has the potential to miss both chronic and occult HBV infection. The most likely explanation for this patient's seropositive OBI is prior history of acute HBV that has resolved or on-going chronic hepatitis B. This finding should caution us to review the management of patients who have lost HBsAg following anti-viral agents. Therefore, the good screening policy should use HBsAg, anti-HBs and anti-HBc total as a screening tool during evaluation. OBI is a clinical conundrum as it is difficult to diagnose and can have a diverse clinical presentation. A high-index of suspicion for OBI is required and screening with HBV PCR should be performed in HBsAg negative and anti-HBc positive patient with signs of chronic or severe hepatic inflammation, cirrhosis or HCC. Several studies indicated that individuals with OBI, who had prior liver injuries or concomitant liver diseases, developed liver adverse events

through either direct or indirect mechanisms. The suggested indirect mechanism involves the mediated immune response that was provoked by the low but persistent viraemia, giving rise to progressive liver damage and eventually liver cancer in the OBI population. OBI retains several of the oncogenic mechanisms of overt HBV, including production of pro-oncogenic proteins and the propensity of the viral DNA to integrate into the host's genome. Further studies on molecular epidemiology and onco-pathogenesis are required to confirm the role of OBI in HCC development, and to determine the mechanisms by which it might exert a pro-oncogenic activity[4]. In a systematic review and meta-analysis study, their conclusions showed a strong association between occult HBV infection and the development of HCC. The OBI-related HCC was associated with a slightly younger population, of age early to mid-60 years. Anti-HBc total, which is associated with the risk of OBI-related HCC, can be used to identify at-risk patients for HCC screening, where appropriate[7].

CONCLUSIONS

We report one patient was diagnosis of intermediate stage HCC, treated with transarterial chemoembolization (TACE) and antiviral treatment with tenofovir disoproxil fumarate (TDF).

Antiviral therapy and surveillance for complications may be warranted once the diagnosis is established. Further work is required to ascertain the clinical significance of otherwise clinically stable patients with OBI with very low DNA levels. It is important to note, however, that low HBV DNA does not guarantee the absence of progressive liver disease[8].

REFERENCES

1. Tokuaki Shobayashi (2023). "The measures against hepatitis in Japan and future direction of measures against hepatitis in Vietnam. Update new progress on hepatitis, cirrhosis and HCC", Journal of Vietnam association for the study of liver diseases, 54: pp. 19-20.

2. Global Burden of Disease Cancer Collaboration. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study, JAMA Oncol., 2017;3: pp. 524-48.

3. Raimondo G, Allain JP, Brunetto MR, et al. (2008). "Statements from the Taormina expert meeting on occult hepatitis B virus infection", J Hepatol., 49: pp. 652-7.

4. Raimondo G, Locarnini S, Pollicino T, et al. (2019). "Update of the statements on biology and clinical impact of occult hepatitis B virus infection", J Hepatol., 71: pp. 397-408.

5. Tan YJ (2011). "Hepatitis B virus infection and the risk of hepatocellular carcinoma", World J Gastroenterol., ;17(44): pp. 4853-7.

6. Makvandi M (2016). "Update on occult hepatitis B virus infection", World J Gastroenterol., 22(39): pp. 8720-34.

7. Chao Weng, Rajneesh Kumar, Rehena Sultana, et al. (2021). "Occult hepatitis B virus infection and the risk of hepatocellular carcinoma: a systematic review and meta-analysis", Dig Med Res., 4:46.

8. Schmeltzer P, Sherman KE (2010). "Occult hepatitis B: clinical implications and treatment decisions", Dig Dis Sci., 55(12): pp. 3328-35.