TOPIC HIGHLIGHT

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Occult hepatitis B virus infection

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Abstract

Occult hepatitis B virus (HBV) infection (OBI) refers to the presence of HBV DNA in the absence of detectable hepatitis B surface antigen. Since OBI was first described in the late 1970s, there has been increasing interest in this topic. The prevalence of OBI varies according to the different endemicity of HBV infection, cohort characteristics, and sensitivity and specificity of the methods used for detection. Although the exact mechanism of OBI has not been proved, intrahepatic persistence of viral covalently closed circular DNA under the host's strong immune suppression of HBV replication and gene expression seems to be a cause. OBI has important clinical significance in several conditions. First, OBI can be transmitted through transfusion, organ transplantation including orthotopic liver transplantation, or hemodialysis. Donor screening before blood transfusion, prophylaxis for high-risk organ transplantation recipients, and dialysis-specific infection-control programs should be considered to reduce the risk of transmission. Second, OBI may reactivate and cause acute hepatitis in immunocompromised patients or those receiving chemotherapy. Close HBV DNA monitoring and timely antiviral treatment can prevent HBV reactivation and consequent clinical deterioration. Third, OBI may contribute to the progression of hepatic fibrosis in patients with chronic liver disease including hepatitis C. Finally, OBI seems to be a risk factor for hepatocellular carcinoma by its direct proto-oncogenic effect and by indirectly causing persistent hepatic inflammation and fibrosis. However, this needs further investigation. We review published reports in the literature to gain an overview of the status of OBI and emphasize the clinical importance of OBI.

Core tip: Occult hepatitis B virus infection (OBI) is defined by the presence of hepatitis B virus (HBV) DNA without detectable hepatitis B surface antigen. The prevalence of OBI varies according to the different endemicity of HBV infection, cohort characteristics, and detection methods. Increasing research on OBI has been conducted with respect to the following: (1) transmission through transfusion, organ transplantation, or hemodialysis; (2) reactivation in an immunosuppression state; (3) contribution to the progression of chronic liver disease; and (4) increased risk for hepatocellular carcinoma. Further studies are needed to establish its clinical significance and management.

INTRODUCTION

Hepatitis B virus (HBV) infection is an important global

public issue. Approximately 2 billion people have serologic markers of HBV worldwide, 360 million of whom have chronic HBV infection. The natural course of HBV infection is determined by the interactions between the host and the virus. Chronic HBV infection is characterized by persistent HBV surface antigen (HBsAg) positivity and viremia. In the past, clearance of HBsAg expression in patients with chronic hepatitis B was considered as disease remission and disappearance of viral DNA[1]. However, the "occult" or "silent" form of HBV infection was first reported in the late 1970s in blood donors with anti-hepatitis B core (anti-HBc) antibody without HBsAg who transmitted hepatitis B[1,2]. The meaning of this clinical entity was reviewed in 1998 by a panel of European and US scientists as a part of the serological pattern "anti-HBc" alone, although the term occult was not used at that time[3]. Increasing data showed persistent low levels of HBV DNA in serum and liver tissues after HBsAg clearance was observed during acute self-limited or chronic HBV infection. Demonstration of this clinical entity has brought about the concept of "occult" or "silent" HBV infection, indicating the presence of HBV DNA in the absence of detectable HBsAg[3,4]. Owing to the development of highly sensitive molecular biology techniques, the clinical and virologic features of occult hepatitis B virus infection (OBI) have been revealed, and its clinical significance has been highlighted recently[5-7]. In this paper, we reviewed the status of OBI with respect to its definition, epidemiology, diagnosis, and mechanism. We also focused on the clinical importance of OBI by focusing on 4 processes: transmission, reactivation, contribution to the progression of hepatic fibrosis, and hepatocellular carcinoma (HCC) occurrence, based on results of available reports.

DEFINITION AND CLASSIFICATION

Several definitions of OBI have been suggested. In the 2008 international workshop held in Italy, OBI was defined as the presence of HBV DNA in the liver (with or without HBV DNA in serum) without HBsAg as determined by using the currently available assays[8]. Serum HBV DNA can be either detectable or undetectable, and when detectable, the level of HBV DNA is usually very low (< 200 IU/mL). When serum HBV DNA levels are comparable to those usually detected in cases of overt HBV infection, "false OBI" should be considered. False OBI is usually due to rare infection with *S* gene escape mutants, which produce a modified HBsAg that is not recognized by routinely used detection assays[9,10]. Defining OBI according to the presence of liver HBV DNA expression is the most accurate because HBV DNA in the liver can be detected even when HBV cannot be detected in serum[11]. However, obtaining hepatic HBV DNA is difficult in clinical practice, and assays for the detection of HBV DNA in liver tissue have not been well standardized[7].

Detection assays for HBV DNA in serum have been used with sufficient sensitivity; therefore, OBI is often defined as the presence of serum HBV DNA without detectable HBsAg in clinical practice and in many studies[7,8,12]. Bréchot *et al*[9] proposed to define occult HBV infection as the detection of HBV DNA by using PCR or other amplification assays in HBsAg-negative individuals. Allain[13] also defined OBI as the presence of HBV DNA without detectable HBsAg, with or without anti-HBc or anti-HBs antibody outside the pre-seroconversion window period. This definition of OBI according to the presence of serum HBV DNA is most commonly used in clinical practice.

OBI has also been defined as a serological condition characterized by the presence of isolated hepatitis B core antigen (anti-HBc) in the absence of HBsAg and anti-HBs antibody[3,14]. Detection of anti-HBc antibody, a surrogate marker of OBI, is useful when an HBV DNA test is not available or when intermittent viremia is suspected[8,15]. However, when OBI is defined according to the presence of anti-HBc antibody alone, false anti-HBc positivity and negativity in the detection of OBI should be considered. Not all anti-HBc-positive subjects are HBV DNA-positive. In addition, the absence of anti-HBc antibody does not exclude seronegative OBI. As mentioned earlier, the definition of OBI slightly differs between studies; thus, cautious interpretation should be exercised when comparing study results about OBI.

OBI can be classified into 2 groups, seropositive OBI [anti-HBc and/or anti-hepatitis B surface (anti-HBs) positive] and seronegative OBI (anti-HBc and anti-HBs negative), on the basis of the HBV antibody profile. Seropositive-OBI develops when serum test results for HBsAg become negative after acute hepatitis or when HBsAg is cleared during the course of chronic hepatitis B. In fact, annual HBsAg seroclearance rates are reported to be 0.50%-2.26% per year in chronic hepatitis B patients, and persistent HBV DNA in the liver was detected in some of these patients[16,17]. Seronegative-OBI is caused by primary occult of anti-HBs or anti-HBc from the beginning of the infection because of the mutation or due to progressive loss of anti-HBs[8,18]. Most OBIs are seropositive OBIs, but > 20% of patients with OBI are seronegative for OBI, representing a population negative for all serum markers of HBV infection[19].

EPIDEMIOLOGY

The prevalence of OBI is reported to range from 1% to 95% worldwide. These prevalence rates are influenced by several factors as follows: (1) geographic differences (endemicity); (2) different patient characteristics, including the presence of comorbid diseases such as chronic hepatitis C; and (3) and the different diagnostic techniques used, which have different sensitivity[8,20,21].

The prevalence of OBI differs according to the endemicity of HBV infection. OBI was reported at a higher rate in an HBV endemic area such as East Asia where 41%-90% of the population had prior exposure to

HBV, and less frequently in the low endemic areas such as North America, where only 5%-20% of the population had previous exposure[22]. Several studies on blood donors with similar cohorts have reported a 0.1%-1.05% prevalence of OBI in HBsAg-negative, anti-HBc-positive donors from North America, 0%-1.59% in donors from Europe, and up to 6% in donors from an endemic area[5,23,24].

The prevalence of OBI differs according to the cohort characteristics. OBI is more commonly noted in patients at high risk for parenterally transmitted infections such as hepatitis C virus (HCV) infection or immunosuppression condition such as human immunodeficiency virus (HIV) infection[25]. In particular, OBI prevalence is high in patients with HCV infection, with HBV DNA detected in approximately 33% of patients with HBsAg-negative HCV infection in Italy and > 50% patients in East Asian countries[19,26,27]. OBI prevalence was also high in patients with other chronic liver diseases at 20%-30%[25,28], in hemophilia patients in Japan at 51%[29], and in intravenous drug users at 45%[30]. Among HIV-infected patients in Turkey, 19.1% of subjects had isolated anti-HBc (considered a marker of OBI) compared to only 2.4% in blood-donor controls[31]. The effect of highly active antiretroviral therapy, clusters of differentiation (CD)4 cell count, and HIV RNA load on OBI prevalence is still controversial[24,32,33].

The prevalence of OBI also differs according to the sensitivity of HBV DNA or HBsAg testing. There are various amplification methods for detecting HBV DNA, and the HBV genome target sites are also different. Some commercial assays are more sensitive than others at detecting HBsAg mutants. The type of sample used (liver or serum) or number of samplings can also have some effect on the diagnosis of OBI. Indeed, as serum HBV DNA levels seem to fluctuate in OBI, serial sample is more useful to identify OBI[21].

Since the study population differs significantly based on the above-mentioned factors, prevalence was hard to compare directly among studies. Therefore, caution should be exercised when interpreting the prevalence of OBI in different studies.

MECHANISM

Some researchers insist the lower sensitivity of the HBsAg immunoassay compared to that of polymerase chain reaction (PCR) for the detection of HBV DNA is responsible for development of OBI. However, this difference in the assay sensitivity cannot explain the characteristic lower replication rate of HBV observed in OBI. The precise underlying mechanisms of OBI are not well understood, which could be multifactorial. Both host and viral factors seem to have roles in suppressing viral replication and infection control[5,19].

Host factors

OBI is characterized a low rate of HBV replication *in*

vivo; however, occult HBV strains are replication-competent *in vitro*. This suggests that host, rather than viral, factors are more responsible for OBI[34]. Similarly, many clinical observations indicate that OBI reactivation sometimes occurs under immunosuppressive conditions, such as during cancer chemotherapy treatment, HIV infection, or hematopoietic stem cell transplantation[25,35]. This can be explained by a break in the balance between the host's immune system and the virus that occurs during occult infection caused by change in immune system function, resulting in reactivation of OBI. These findings strongly indicate the critical role of the host's immune system in development of OBI.

Other *in vitro* studies showed vigorous antiviral T-cell responses several years after clinical recovery from acute hepatitis B. This suggests persistent synthesis of minute undetectable amounts of virus by HBV covalently closed circular DNA (cccDNA) or other viral transcripts in OBI, maintaining the HBV-specific memory T-cell response[36]. Therefore, these findings also indirectly emphasize the role of the host immune system in the development and maintenance of OBI[25,37,38].

In addition to memory T-cell immune reaction, innate immune system or cytokines such as tumor necrosis factor-α and interferon-γ also have been reported to be associated with OBI[39,40]. Furthermore, epigenetic regulation, including DNA methylation of the HBV genome and posttranslational modification of histones, has been reported to be related to the OBI[41].

Viral factors

Although there is no sufficient evidence, viral factors also seem to have some effect on development of OBI. Several possible mechanisms explaining the low viral replication rate in OBI have been demonstrated. Mutations of the X region of HBV reduce the ability of the X protein to transactivate host cellular proteins that are essential for viral replication, which led to the suppression of replication and expression of HBV DNA, and resulted in negative seropositivity for HBsAg[42]. Escape mutation of the S region was another possible viral factor associated with OBI, which also decreases reactivity in HBsAg detection assays[43]. In addition, a large number of mutations were reported which can reduce HBsAg expression, decrease immune recognition of the virus, and impair HBV packaging. However, cautious interpretation is necessary, as most of these studies lacked a control group or mutations appeared not only in patients with OBI but also those with overt HBV infections. Further studies should be conducted[44].

DIAGNOSIS

Several methods using liver tissue, DNA extracts from liver or blood, or other serologic markers such as anti-HBc IgG have been used to diagnose OBI. The gold standard for OBI diagnosis is the detection of HBV DNA in the DNA extraction from the liver, as cccDNA

persists in the hepatocytes and HBV DNA is sometimes detected in the liver in the absence of HBV DNA in the serum. However, obtaining liver tissue is an invasive procedure; therefore, obtaining hepatic HBV DNA is difficult in clinical practice. In addition, real-time PCR-based assays for serum (or plasma) HBV DNA detection have been used with sufficient sensitivity to detect OBI in many cases; hence, serum HBV DNA assays are widely used to diagnose OBI[8].

DNA should be extracted from samples using the most efficient procedure. A higher rate of HBV DNA detection has been obtained with snap-frozen liver tissue than with paraffin-embedded liver tissue. When a blood sample is used, at least 1 mL of serum should be collected to improve the sensitivity of the test. DNA extracts should be amplified by highly sensitive nested PCR or by a real-time PCR technique that can detect fewer than 10 copies of HBV DNA using the oligonucleotide primers specific for different HBV genomic regions and complementary to highly conserved nucleotide sequences. Appropriate negative and positive controls should be included in each PCR experiment. In addition, periodic testing for HBV DNA will improve diagnosis of OBI especially in high-risk patients, as intermittent viremia can occur in occult HBV infection[8,18,21,22,45].

When highly sensitive HBV DNA testing cannot be performed, anti-HBc could be used as a possible surrogate marker for identifying potential seropositive OBI in cases of blood and organ donation or those receiving immunosuppressive therapy. In this case, seronegative OBI or false-negative anti-HBc in an immunocompromised host should also be considered[45].

CLINICAL SIGNIFICANCE

Transmission of OBI

Transfusion: Although the risk of HBV transmission through blood transfusion has decreased owing to the development of sensitive and specific diagnostic assays, transfusional transmission of HBV still occurs. Transmission of HBV by transfusion occurs in 3 situations: (1) blood from a donor with OBI; (2) blood from patients in the infectious window period of HBV infection; or (3) blood from a donor infected with S-escape mutant HBV infection not detected by the routinely used diagnostic HBsAg assay. The prevalence of OBI in blood donors is variable depending on the geographic area, and is higher in HBV endemic areas[46]. In an Australian study analyzing 2673521 blood donors, the incidence of OBI was approximately 5.55 per 100000 donors compared to the 1.06 per 100000 donors with an acute serologic window period infections[47]. In China, the pooled prevalence of OBI among donors was 0.094%[48]. In Europe, OBIs are detected in 1:2000 to 1:20000 samples donated[45,49-52].

The infectivity of OBI by transfusion is determined not only by the viral load or the volume of plasma but also by the HBV serological status (anti-HBc and/or anti-HBs). The risk of HBV transmission may depend on the presence of anti-HBsAb. Among occult HBV-infected donors, those with high anti-HBs levels (recovered) are unlikely to transmit the infection, whereas those without anti-HBs (anti-HBc only) may transmit the infection[53,54]. However, the infectivity of anti-HBs-containing blood components in immunodeficient or immunosuppressed recipients has not been systematically explored. Considering that immunocompromised hosts represent a substantial proportion of transfusion recipients, caution should be exercised when anti-HBc-positive blood is transfused to immunocompromised recipients, even when anti-HBs positive[45,54].

Nucleic acid testing (NAT) for donor screening detects HBV infection in the window period (before the appearance of HBsAg) as well as OBI, indicating the presence of HBV DNA in the absence of HBsAg. Therefore, the introduction of NAT has further decreased the risk of HBV transmission through blood transfusion. However, cost effectiveness and availability of NAT should be considered before clinical application. Where HBV DNA testing is not available, such as in developing countries, testing for anti-HBc is strongly recommended[8,45,55].

Organ transplantation: OBI in a transplantation donor is important because there is a risk of HBV transmission from an OBI-seropositive donor, and severe HBV reactivation can occur in some of these cases during immunosuppression. As the hepatocytes are the reservoir of HBV cccDNA, the rate of transmission is higher in orthotopic liver transplantation compared to other organ transplantations such as kidney, bone marrow, and heart[25,56]. The transmission of HBV infection from HBsAg negative/anti-HBc positive (considered OBI) donors to recipients were reported at a rate of 17%-94%[57-59]. Because of this high risk of transmission, prophylaxis is recommended to prevent HBV reactivation. Although not directly compared in randomized controlled trials, the combination of antiviral and hepatitis B immunoglobulin seems to be superior to treatment with antiviral or hepatitis B immunoglobulin monotherapies as prophylaxis. Lamivudine is the most widely used antiviral, and studies using newer antivirals such as entecavir, adefovir, and tenofovir are few[57]. It is uncertain whether OBI is transmitted from HBV-seronegative donors.

OBI in liver transplant recipients is also important. The etiology of *de novo* HBV infection after liver transplantation was traced to OBI in both donors and recipients[60].

Hemodialysis: Hemodialysis patients are at increased risk of parenterally transmitted infections because they are in an immunosuppressed state and exposed to invasive procedures, share the same dialysis machine, and receive more transfusions than the general population. The relatively low acceptance and response rates to the HBV vaccine among dialysis patients also likely contributes to OBI transmission in hemodialysis patients[55,61]. The prevalence of OBI in hemodialysis patients varies from 0%

to 54% according to the diagnostic techniques or HBV endemicity[62,63], and several studies suggest that OBI could be a source of viral spread both to other patients and staff within the hemodialysis units[61,62]. Therefore, patients and staff need HBV vaccine boosts to maintain levels of protective antibody to HBsAg (anti-HBs). Strict dialysis-specific infection-control programs, including avoidance of dialyzer reuse and use of dedicated dialysis rooms and machines, should be implemented. Staff for infected patients should be educated on preventive method to limit HBV transmission within dialysis units. Furthermore, regular screening for HBV DNA with sensitive PCR-based assays in all dialysis patients should be considered, and more attention should be given to patients who receive immunosuppressant drugs after renal transplantation[62,64].

Pregnancy and OBI transmission: Kwon *et al*[65] studied the possibility of transmission of OBI to the fetus in 202 healthy pregnant women. Among these, six (3%) women were OBI positive. When cord blood of 4 of these 6 women was evaluated for HBV DNA, all were HBV-DNA negative. This result suggests that vertical transmission through the cord blood is negligible, but this needs to be investigated further[65].

Reactivation

HBV reactivation after systemic chemotherapy was first reported in the mid 1970's, and thereafter, HBV reactivation has been reported not only in HBsAg-positive patients but also in OBI patients[35,66]. Although, reactivation in OBI occurs more rarely than in HBsAg positive patients, HBV reactivation is quite a frequent event in immunocompromised OBI patients when including not only symptomatic hepatitis but also HBsAg re-seroconversion in the reactivation of OBI[66-68]. This finding is clinically important because it can be associated with liver dysfunction, sometimes causing life-threatening fulminant hepatic failure, and often requires interruption of chemotherapy[20,69]. The underlying mechanism of reactivation is thought that chemotherapy induced immunosuppressive state triggers rapid viral replication because of the loss of the immunological control. After immune system reconstitution, cytotoxic T-cell-mediated hepatocyte injury may occur, leading to the development of hepatic inflammation and concomitant hepatic necrosis.

Hematological malignancies, hematopoietic stem cell transplantation, liver transplantation from anti-HBc positive donors, and treatment with anti-CD20 (rituximab) seem to be the factors associated with the highest risk of OBI reactivation[25,70-73]. Other immunosuppressive conditions, including HIV infection, kidney or bone marrow transplantation, systemic chemotherapy, and rheumatologic diseases or inflammatory bowel disease treated with biological agents or high-dose steroids for prolonged treatment, also have been reported as possible causes of viral reactivation in OBI patients[37].

While prophylactic antiviral treatment to prevent re-

activation is well established in HBsAg-positive patients undergoing immunosuppressive therapies, its use in OBI patients is debatable[25,70]. In highly endemic areas, 20% of cancer patients have been reported to be HBsAg-negative and anti-HBc positive[74]; thus, prophylactic antiviral use for all OBI patients is unlikely to be cost-effective[68]. On the contrary, delayed treatment with an antiviral may be fatal, and frequent monitoring for reactivation in OBI patients is sometimes difficult. Therefore, use of antivirals is recommended for OBI patients with highest risk of reactivation (previously suggested) regardless of HBV DNA presence and when HBV DNA monitoring is unavailable in routine practice[70,73,75,76]. HBsAg-negative and anti-HBc-positive patients with undetectable or low levels of HBV DNA without highest risk of reactivation should be carefully monitored using alanine aminotransferase (ALT) and HBV DNA levels, with adequate intervals before and during immunosuppressive treatments, and also for several months after stopping treatment. In this case, antiviral treatment should be started as soon as HBV reactivation is detected, before ALT level elevation, since the objective of this strict surveillance is to identify HBV reactivation early before liver injury to prevent acute hepatitis[68,75]. Among antivirals, lamivudine seems to be effective in patients with no or very low serum HBV DNA levels[77]. More potent nucleoside analogues should be chosen when reactivation is confirmed or lamivudine resistance is suggested[73]. Currently, there is no consensus about the optimal duration of preventive antiviral therapy[78]. However, several reports suggest the start of prophylaxis 1-2 wk before the start of immunosuppressive therapy and prolonged antiviral therapy at least 6-12 mo after completion of chemo- or immunotherapy to prevent delayed reactivation of HBV[79,80]. However, further studies should be performed to determine the optimal duration of treatment.

Progression of chronic liver disease

It has been shown that HBV genomes may persist for a long time in the liver, inducing mild necro-inflammation in patients after complete clinical recovery from acute self-limited hepatitis B[81]. An *in vivo* study of a woodchuck model showed similar results; animals that recovered from acute woodchuck hepatitis virus (the rodent HBV-like hepadnavirus) showed lifelong existence of viruses replicating at low levels, inducing mild persistent liver necroinflammation[82]. These results suggest the role of OBI in the progression of chronic liver disease, and there has been much interest in the clinical impact of OBI, both as a mono-infection and as co-infection with HCV, on the course of chronic liver disease.

As HBV and HCV share the same transmission route, OBI is highly prevalent in patients with HCV-related chronic hepatitis. Thus, many cross-sectional studies investigated the influence of OBI on the outcome of chronic hepatitis C. Previous studies showed OBI as a risk factor for more severe liver disease[26,83]; however, the cross-sectional nature of most of these studies could

have biased patient selection. A recent longitudinal Italian cohort study by Squadrito *et al*[84] showed that among chronic hepatitis C patients, patients with OBI had higher risk of progression to cirrhosis, development of HCC, and increased risk of liver-related death compared to OBI-negative patients[84]. Other studies additionally showed the association of ALT level flares with detection of HBV DNA in HCV-OBI co-infected patients, indicating that transient HBV reactivation might be involved in liver injury in these patients[85,86]. A recent meta-analysis of both OBI mono-infection and co-infection with HCV showed that OBI is associated with chronic liver disease, with an overall 8.9-fold increased risk compared to individuals without OBI. Subgroup analysis comparing HCV-positive and -negative subjects showed that HCV-positive as well as HCV-negative patients (cryptogenic liver disease) had increased risk for chronic liver disease[87].

Conclusively, when OBI is present with HCV or with other chronic liver diseases, hepatic inflammation induced by a mild immune response to OBI may accelerate liver injury. In most healthy subjects under immune control, it is not determined yet whether OBI can cause clinically relevant hepatic damage[70,88].

Hepatocellular carcinoma occurrence

HBV infection is known to be one of the most important risk factors in the development of HCC. Although the mechanism by which HBV infection causes HCC is not completely known, HBV causes HCC both indirectly and directly. HBV infection causes hepatic inflammation, regeneration, and fibrosis associated with cirrhosis, which indirectly contribute to HCC development. In a direct pathway, HBV integrates into the host genomes, produces proteins with pro-oncogenic activities, such as X protein and mutant preS-S proteins, and causes genetic and epigenetic alterations that may directly induce hepatocyte transformation[89,90].

Considering that OBI is characterized by intrahepatic persistence of viral cccDNA, OBI can be a risk factor for HCC development in a similar way. In epidemiologic studies, a significantly higher prevalence of OBI was observed in HCV-positive HCC patients than in HCV-positive populations without HCC. Similar results were reported in the HCV-negative patients with cryptogenic liver disease or alcoholic liver disease[37,91-94]. An *in vivo* experimental study also demonstrated that woodchucks, after serological recovery from acute woodchuck hepatitis virus infections, are at high risk of developing HCC even after apparent clearance of the virus[95]. In prospective studies, the cumulative probability of developing HCC was significantly higher among patients with OBI than among HBV DNA-negative patients, both in the presence[96-99] or absence of HCV infection[100]. In addition, a recent meta-analysis demonstrated that OBI increases the risk of HCC in both HCV and non-HCV infected patients[101].

Although these results support the idea that OBI is a risk factor for HCC, caution should be exercised during interpretation[102]. First, as most of the study subjects had chronic liver disease of various etiologies, these results indicate OBI as a co-carcinogen of HCC in addition to other suggested carcinogens such as previous HBV infection, HCV, or alcohol. The role of OBI *per se* in the occurrence of HCC should be further investigated. Second, further studies should be performed to confirm the role of OBI in cryptogenic liver disease. Previous studies have considered heterogeneous definitions of cryptogenic liver disease and non-B non-C liver diseases, (*e.g.*, not differentiating nonalcoholic fatty liver disease and sometimes including alcohol or autoimmune liver disease in cryptogenic liver disease); therefore, it is difficult to interpret the results. Third, several other studies did not find an association between OBI and HCC, and ethnic and epidemiologic differences should be considered in the interpretation of the results[103].

CONCLUSION

OBI, defined as the presence of HBV DNA without detectable HBsAg, has recently gained increasing attention. Although the exact mechanism of OBI has not been determined, OBI can be transmitted, cause reactivation of HBV, and contribute to the development of progressive liver disease and HCC. Thus, physicians should focus on the appropriate management of these patients, and further studies to clarify the clinical significance of OBI are needed.

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