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Occult Hepatitis B in Patients Undergoing Chemotherapy

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Abstract

Introduction: The hepatitis B virus (HBV) is one health problem in Iran. Occult hepatitis B (OBI) is diagnosed by the detection of HBV DNA in the serum or liver tissue of patients for whom other serology, especially HBsAg and HBcAg, are negative. The current study aimed to determine the prevalence of OBI in patients who refer for chemotherapy.

Methods: All patients referring for chemotherapy to the oncology clinic of Baqiyatallah Hospital in Tehran, Iran from 2012 to 2013 were selected as the population of this cross-sectional study. Samples of 5 mL of blood were taken from each subject and assayed for HBsAg and HBcAb. If HBV markers were negative, a qualitative HBV DNA PCR was done to detect OBI. The data was analyzed using SPSS 17 software, and the frequency test was used to determine prevalence.

Results: In this study, 251 candidates for chemotherapy were recruited. Of this number, 114 (45%) patients were women. Mean patient age was 52.6 years. A total of 149 (59%) study subjects were employed, and the others were housekeepers or self-employed. About 67 (26.6%) patients had a history of one dose and 40 (15.9%) patients had a history of complete HBV vaccination. HBsAg was positive in 6 (2.4%) and HBcAb was positive in 33 (13.1%) patients; qualatative HBV DNA PCR was positive in 2 (0.8%) patients.

Conclusion: This study revealed that OBI infection has a low prevalence, but patients referring for chemotherapy are at risk for its reactivation. On the other hand, isolated HBcAb is also a risk factor; therefore, in addition to HBsAg, it is recommended that HBcAb be evaluated before chemotherapy.

Keywords: Hepatitis B on, Occult hepatitis B, Hepatitis B core antibody, HBsAg, Cancer, Chemotherapy

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Introduction

Hepatitis B virus (HBV) infection is a worldwide health problem with nearly 2 billion people infected, although it has caused less than one million deaths.[1] HBV presents as an asymptomatic, acute symptomatic, chronic carrier, chronic active hepatitis, and rarely as fulminant hepatitis.[2] Occult hepatitis B (OBI) is diagnosed by the detection of HBV DNA in the serum or liver tissue of patients whose other serology assays, especially HBsAg and HBcAg, are negative. Some studies, however, have shown HBV DNA along with positive HBcAb and negative HBsAg to be OBI; therefore, solely HBcAb and DNA HBV positive results suggest that people with OBI can transmit the hepatitis B virus to others. This harbors risks for HBV transmission through hemodialysis, blood donation, and organ transplant.[3,4] OBI resembles a usual infection. It may be reactive and progress to acute or chronic hepatitis or slowly to cirrhosis, and sometimes to hepatoma.[5] Moreover, it may be reactive after immunosuppresive therapy.[6,7] OBI can slowly progress to cirrhosis; therefore, it can be difficult to diagnosis and needs highly sensitive real-time PCR assay to detect less than 200 copies/Lt of HBA DNA in serum. Nested PCR is more highly sensitive than qualitative or real-time PCR, and it is recommended as a more reliable assay for the detection of OBI.[8] Most cases of OBI may be reactive in high risk patients such as those with HIV, those undergoing immunosuppression, organ transplant, or chemotherapy, and

in those with a malignancy.

The prevalence of HBV infection differs by geographical region. It has a high precvalence in China and sub-Sahran Africa, but its prevalence is low in Iran. Prevalence rates of OBI also differ based on the prevalence of chronic HBV infection. In Iran, prevalence rates range from 0.8% to more than 2.7% in some provinces.[9,10] Because patients undergoing chemotherapy are at risk for the reactivation of occult hepatitis, the aim of the current study was to evaluate the prevalence of OBI in patients referring for chemotherapy.

Methods

All patients referring for chemotherapy at the oncology clinic of Baqiyatallah University of Medical Sciences in Tehran, Iran from 2012-2013 were selected as the study population. From each participant, 5 mL samples of whole blood were drawn; its serum was separated in the field by centrifugation at 4000/rpm for 5 minutes, and then the samples were stored at -20°C until assay. Laboratory tests were done by Baqiyatallah Hospital Laboratory.

Exclusion criteria included a history of HIV infection, HBV, HCV, homosexuality, intravenous drug abusers, the simultaneous existence of other immunodeficiency diseases, those undergoing immunosuppressive therapy, and those under treatment for chronic hepatitis.

HBsAg was examined using ELISA kits manufactured by Organon Technika, Holland. HBcAb was also examined using ELISA kit (bioELISA anti HBc, Biokit, Barcelona, Spain). If these 2 HBV markers were negative, then a qualitative HBV DNA PCR by viral nucleic acid kit (Roche, Germany) was done to detect DNA of the HBV in the patients' serum, which would distingush OBI.

The data was analyzed using SPSS 17 software, the frequency test was used to determine prevalence, and qualitative varients were assayed using the chi-square test. A P value <0.05 was considered statistically significant.

Results

In the current study, 251 patients who were candidates for chemotherapy were recruited; 114 (45%) subjects were women, and the mean patient age was 52.6 years (range = 14-83 years). About 149 (59%) were employed, and all others were housekeepers or self-employed.

About 206 (82%) subjects in this study had a high school or higher education level. About 67 (26.6%) subjects had a history of one dose and 40 (15.9%) had a history of complete HBV vaccination. All others were negative for vaccination (Table 1).

HBsAg was positive in 6 (2.4%) patients, and HBcAb was positive in 33 (13.1%) patients. Between HBsAg and HBcAb,a significant association was seen (P<0.05). Quantitative HBV DNA PCR was positive in 2 (0.8%) subjects. No other varients were associated with HBcAb, HBsAg, or HBV DNA PCR (Table 2).

Table 1. Demographic Data of Patients

Variable		No.	%
Gender	Men	137	55
	Women	114	45
Surgery history	Positive	168	67
	Negative	82	33
HBV vaccination	One dose	67	26.6
	Three doses	40	15.9
	Negative	169	67
Blood transfusion	Positive	76	30
	Negative	137	54
HBV in family	Positive	9	3.6
	Negative	242	96.4
Eduction level	>Diploma	206	82
	< Diploma	45	18
Employee	Yes	149	59
	No	102	41
Hepatomegaly	Yes	40	16
	No	211	84

Table 2. Prevalence of Hepatitis Infection Markers

		No.	%
HBsAg	Positive	6	2.4
	Negative	245	97.6
HBcAb	Positive	33	13
	Negative	218	87
HBeAb	Positive	24	9.6
	Negative	227	90.4
HBV DNA PCR	Positive	2	0.8
	Negative	249	99.2

Discussion

Some studies have shown that after several courses of chemotherapy, most HBsAg-positive patients experience a reactivation of hepatitis. For this reason, this problem was also evaluated in chemotherapy patients.[11]

In malignancy patients undergoing chemotherapy who had positive markers for the HBV, prophylaxis with antiviral medication is recommended.[12] Hematological malignancies may be more reactive to occult hepatitis than solid tumors, but in the present study, the association between occult hepatitis and type of malignancy was not significant. This result may depend upon the type of chemotherapy, but this area was not evaluated in this study.[13] This study found the prevalence of OBI to be very low, i.e. about 0.8%. Compared to other studies, it is due to difference in prevalence of the HBV in any province of Iran.[10,14] Iran has a low prevalence, but in some provinces, the prevalence is high; therefore, OBI may also have a high prevalence in those provinces.[15]

Another reason for the low prevalence of OBI in Iran is the routine vaccination against the HBV in children and the prevention of HBV infection.[16] HBV vaccination in high risk adults also increased immunity, even when vaccination was incomplete. This is one important reason for the low prevalence of OBI in Iran. This study found that more than 42.6% of subjects had a history of HBV vaccination.[17]

Similar to the current study, a study in China demonstrated that after chemotherapy, hepatitis B infection was reactivated and the viral load was increased in HbsAg negative patients. The authors of that study recommended that consideration be given to high risk patients for HBV infection and that therapy for HBV infection should be begun before chemotherapy, lamivudine is highly recommended for prophylaxis, and it can prevent flare-ups of hepatitis B infection after chemotherapy.[18] The prevalence of OBI is low in Iran, but its prevalence rate is higher in China at 3.2%,[18] Italy at 3.6%,[19] Canada at 1.2%,[20] and Hong Kong at 15%.[21] This difference is dependent upon the high prevalence of chronic hepatitis B.

In the current study, the prevalence of OBI was not different between men and women. This result is opposite that of other studies which have shown that women comprise a high-risk group and more healthcare is recommended for them.[22]

HBcAb is one of the HBV infections that is described by three conditions in infected people: first is the window period, second is late infection which may be the recovery phase, and third is late infection that can be progressive. Thus, it is important in immunosuppressed patients.[23] The IgM and IgG of HBcAb have different risks for the reactivation of hepatitis or the transmission of the HBV through blood donation. A positive IgM HBcAb can represent acute and recent HBV infection, and blood transmission to others or chemotherapy could be dangerous. However, a positive IgG HBcAb may show recovery from hepatitis B, although the risk of reactivation of hepatitis B infection cannot be identified, because it may suggest OBI.[23,24]

In the current study, the prevalence of HBcAb was more than 13% which is lower than that in other studies such as Raimondo 50%[19] and Moghaddam 20.2%[23]; however, it should be considered as a risk factor in chemotherapy patients.[25]

Patients with a positive HBV vaccination who had only HBcAb are at risk for reactivation of the hepatitis B infection in patients undergoing chemotherapy; therefore, isolated HBcAb should be considered before chemotherapy.[26]

In the current study, two patients had a positive DNA PCR result, and aspartate aminotransferase and alanine aminotransferase increased after chemotherapy. Antiviral therapy was begun and prevented hepatic failure, similar to another study that recommended antiviral treatment in high risk patients with HBsAg and HBcAb or only HBV DNA positive. This was also similar to another study which found that the reactivation of hepatitis B infection may be asymptomatic with only increased liver enzymes and could cause fulminant hepatitis and ultimately death. Therefore, the administration of prophylactic drugs such as lamivudine is recommended prior to beginning chemotherapy.[27]

Although HBsAg is a standard screening test for HBV infection, only 2.4% of the patients in the current study had a positive HBsAg, whereas more than 13% had a positive HBcAb. The recent test is more sensitive and can determine which patients are more susceptible for the reactivation of hepatitis B infection after chemotherapy.[28]

Treatments other than chemotherapy, such as prolonged and high-dose steroid use, can also reactivate hepatitis, and the screening of HBsAg and HBcAb in immunocompromised patients is recommended.[29]

Because chemotherapy in occult hepatitis can reactive hepatitis and can sometimes cause fulminant hepatitis, although the prevalence of OBI is very low as the low prevalence of chronic hepatitis B in Iran, patients that should take chemotherapy are recommended to have HBV DNA PCR[30] before chemotherapy.[31,32]

In the current study, the prevalence rates of OBI and HBcAb had no significant association with gender or age, opposite to some other studies in which the prevalence of HBV infection was higher in homosexuals or intravenous drug abusers; albeit these groups were excluded from the current study.[33]

This study showed that the association between job and OBI and HBcAb was not significant, but in another study, it was higher among white-collar workers and lowest among agriculture workers, that it is due to low sample size of studies.[34]

It has been reported that the prevalence of hepatitis B infection was lower among people with a high level of education than among those with a low level of education, but this could not be confirmed in the current study.[35]

Some studies have shown that the prevalence of OBI was higher in some malignancies such as solid tumor or in patients undergoing chemotherapy containing steroids, but in the present study, it was not detected.[36] The present study did not demonstrate any difference in the prevalence of OBI between men and women, opposite to the study of Lok et al that suggested men were at greater risk for the reactivation of hepatitis after chemotherapy; thus, Lok et al recommended that high risk men should be assayed for HBV infection before beginning chemotherapy.[37]

One limitation of this study was that it was impossible to assay nested PCR HBV DNA, because the project's budget was insufficient. Qualitative HBV DNA PCR may have falsely decreased the prevalence of OBI, and it is a life-threatening risk for patients who are candidates for chemotherapy.

Conclusion

This study revealed that OBI has a low prevalence in this population, and patients who refer for chemotherapy are at risk for reactivation of the HBV infection. Moreover, isolated HBcAb is also a risk factor and may be reactive after chemotherapy; therefore, it is recommended that HBcAb be evaluated for HBV infection before chemotherapy is begun. Simultaneously assaying HBsAg and HBcAb before beginning chemotherapy can diminish the reactivation of the HBV infection. In patients at a high risk for HBV infection, the highly sensitive nested quantities DNA PCR assay is advised before chemotherapy. Chemotherapy patients with OBI or only a positive HBcAb should be considered for accurate observation or antiviral therapy.

Research Highlights

What Is Already Known?

Hepatitis B virus (HBV) infection is a worldwide public health problem with nearly 2 billion people infected. Occult hepatitis B (OBI) is diagnosed by the presence of HBV DNA in the serum or liver tissue of patients whose other serology assays are negative. On other hand, malignancy prevalence also is high and chemotherapy can induced immune deficiency and caused activation of reactive occult B hepatitis, cirrhosis and rarely fulminant hepatitis. Therefore, we should be considered occult B hepatitis as a threat for any patients candidate for chemotherapy.

What This Study Adds?

Our knowledge/study indicated, the presence of 13% HbcAb and 0.8% HBV DNA positive in blood of patients candidate for chemotherapy. Hence, before chemotherapy in patients had malignancy, we should be checked hepatitis B virus serology and HBV DNA PCR for prevention of reactivation of hepatitis B in time of chemotherapy.

Authors' Contributions

All authors contributed equally to this study.

Conflict of Interest Disclosures

None.

Ethical Approval

This study was approved by the Ethics Committee of Baqiyatallah University (NO: 826-1394), and written informed consent was obtained from all patients prior to recruitment to the study. For each subject, complete demographic data including age, education level, job, and type of malignancy, was collected.

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