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# PREVALENCE OF OCCULT HEPATITIS B INFECTION IN IRANIAN CANCER PATIENTS BEFORE CHEMOTHERAPY TREATMENT

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**ABSTRACT** - ***Background*** - Occult hepatitis B infection is characterized by negative hepatitis B surface antigen (HBsAg) and also detectable hepatitis B virus (HBV) -DNA, with or without hepatitis B core antibody (anti-HBc). HBV reactivation in individuals under immunosuppressive therapy is critical, occurring in occult HBV. ***Objective*** - In this study, we aimed to determine the prevalence of occult HBV infection among hepatitis B surface antigen negative in cancer patients before receiving chemotherapy. ***Methods*** - Sera from 204 cancer patients who were negative for HBsAg, were tested for anti-HBc antibodies. The samples that were negative for HBsAg but positive for anti-HBc also examined for HBV-DNA by polymerase chain reaction (PCR). ***Results*** - Of the 204 HBsAg negative blood samples, 11 (5.4%) samples were positive for anti-HBc antibodies. HBV-DNA was detected in 9/11 (81%) of anti-HBc positive samples. Occult HBV infection in hematological cancers was more than solid cancers, 4.8% and 4.3% respectively. There was no significant difference in HBc antibody positivity based on vaccination, previous blood transfusions, history of familial hepatitis or biochemical parameters (ALT, AST, total and direct bilirubin levels) ($P$>0.05). ***Conclusion*** - Screening of occult HBV infection by HBsAg, HBV DNA and anti HB core antibody should be suggested as a routine investigation in cancer patients before receiving chemotherapy.

**HEADINGS** – Hepatocellular carcinoma. Hepatitis B virus. Viral DNA. Hepatitis B antibodies. Hepatitis B core antigens.

## INTRODUCTION

Hepatitis B virus (HBV) infection is a serious health problem, which has damaged nearly two billion people all around the world, despite the identification of the vaccine strain. There are approximately 350-400 million HBV carriers in the world and every year, around one million people die from HBV-related hepatic failure[21,30].

Occult hepatitis B virus infection is one of the enigmatic and crucial types of hepatitis B infection, which is normally identified by negative serum hepatitis B surface antigen (HBsAg) and detectable HBV-DNA in the liver and/or serum, with or without hepatitis B core antibody (anti-HBc)[31]. Occult HBV infection (OBI) is basically resulted from a continuous suppression of viral replication and gene expression. It is typically exposed in the majority of patients with the positivity of antibody against HBV core antigen (anti-HBc)[25,31]. It has been demonstrated that 20% of occult HBV infections are negative for all HBV serological markers, even though the number of HBV DNA was found four, the HBV viral load was generally low[28].

This finding suggests that the diagnosis of OBI can be difficult due to the very low amounts of viral DNA (<200 IU/mL) in the infected persons without detectable HBsAg[35]. The individuals with an OBI undergoing immunosuppression are generally at risk of HBV reactivation. As emphasized by Allain, the severity of immunosuppression and its period showed a significant role in the initiation of the reactivation of HBV infection[3].

It is worth mentioning that the virological and clinical reactivation of occult HBV infection has been frequently discovered in various clinical adjustments, such as HIV infection, hematologic cancer, hematopoietic stem cell, and organ transplantation[6,30,39]. In such situations, HBV reactivation has a mortality rate close to 20 percent, because of the liver failure or the development of the primary disease due to the discontinuation of unique treatment method[1,18,37].

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When HBV reactivation happens in connection to chemotherapy among the patients with cancer, a future treatment distraction or an early termination might negatively affect the treatment results[5,13,17]. Chemotherapy may contribute to an increase in virus replication and infection of more hepatocytes in the lack of an active host immune reaction[37].

Based on our available information, only few investigations have been performed concerning the prevalence of occult HBV infection in cancer patients, before they receive chemotherapy[4,22]. Several studies have revealed the raised prevalence and reactivation in cancer patients[2,24]. In this study, it is intended to estimate the prevalence of occult HBV infection in hematologic and solid cancers. Before chemotherapy, through utilizing serum HBV-DNA as a screening tool, it is also used for anti-HB core antibody testing.

## METHODS

### Patients

This cross-sectional study included 204 patients with hematological and solid cancer before receiving chemotherapy. Patients of this study were selected from the Oncology Departments of Yazd Shahid Sadoughi University School of Medicine, from April 2013 to February 2015. All patients included were negative for HBsAg. Participation in the research was voluntary after an informed written permission was received from the patients before the study. All individuals were asked issues concerning age, sex, type of cancers (haematological or solid), blood transfusion, haemodialysis, jaundice and history of hepatitis B vaccination. Before start of the cancer therapy each patient underwent full history taking, total physical examination, routine biochemistry assays including alanine transaminase (ALT), aspartate transaminase (AST), total and direct bilirubin. Patients with HBV infection as labeled by positive HBsAg were excluded.

Venous blood samples for occult hepatitis B infection (OBI) were obtained from all patients. Samples were tested for hepatitis B core antibody (HBcAb) and HBsAg using a commercially available enzyme-linked immunosorbent assay (LOT NO.C3T2/15, Italy). All serological tests were performed as instructed by the manufacturers. The samples that were negative for HBsAg but positive for anti-HBc markers also examined for the presence of HBV-DNA by PCR.

Patients who were HBsAg negative, HBc antibody positive and serum HBV DNA positive (>50 IU/mL, according to kit inc) were labelled as occult hepatitis B infection (OBI).

### Statistical analyses

The SPSS software version 16.0 and chi-square test were used for data analysis. The significance level was $P<0.05$.

## RESULTS

Of the 204 sera, 11 (5.3%) sera, including 5 (2.4%) males and 6 (2.9%) females, were positive for HBcAb ($P>0.05$). Of these 11 patients, 9 of 204 were positive for HBV DNA by PCR. The prevalence of HBV DNA among the two genders was four (1.9%) in male and five (2.4%) in female patients ($P>0.05$). (Table 1).

The frequency of OBI among the Cancer groups was 63 (30.9%) cases of haematological, 141 (69.1%) cases of solid cancer, occult HBV infection in hematological cancers was more as compared to solid cancers, 4.8% and 4.3% respectively ($P>0.05$). (Table 2).

There was no significant difference in HBc antibody positivity based on vaccination, previous blood transfusions (BT), history of familial hepatitis or biochemical parameters (ALT, AST, Total and direct bilirubin) levels ($P>0.05$) (Table 3 and 4).

**TABLE 1.** Distribution Pattern of HBcAb positive and negative patients between the two genders

| Variables | HBcAb positive | | HBcAb negative | Total |
|---|---|---|---|---|
| | HBV DNA negative | HBV DNA positive | | |
| Age | 63.50 ± 4.94 | 65.55 ± 14.72 | 51.57±19.49 | 52.43 ± 18.47 |
| Male | 1 (1 %) | 4 (3.9 %) | 97 (95.1 %) | 102 (100%) |
| Female | 1 (1%) | 5 (4.9 %) | 96 (94.1 %) | 102 (100%) |
| Total | 2 (1%) | 9 (4.4%) | 193 (94.6%) | 204 (100) |

HBcAb: hepatitis B core antibody; HBV: hepatitis B virus.

**TABLE 2.** Distribution pattern of HBcAb positive and negative patients between the two types of malignancy

| Malignancy | HBcAb positive | | HBcAb negative | Total |
|---|---|---|---|---|
| | HBV DNA negative | HBV DNA positive | | |
| Haematological | 0 (0%) | 3 (4.8%) | 60 (95.2%) | 63 (100%) |
| Solid | 2 (1.4%) | 6 (4.3%) | 133 (94.3%) | 141 (100%) |
| Total | 2 (1%) | 9 (4.4%) | 193 (94.6%) | 204 (100%) |

HBcAb: hepatitis B core antibody; HBV: hepatitis B virus.

**TABLE 3.** Distribution pattern of HBV positive and negative patients based on vaccination, previous blood transfusions and history of familial hepatitis

| Historical Status | HBcAb positive | | HBcAb negative | Total |
|---|---|---|---|---|
| | HBV DNA negative | HBV DNA positive | | |
| Vaccination | | | | |
| Yes | 0 (0%) | 0 (0%) | 47 (100%) | 47 (100%) |
| No | 2 (1.3%) | 9 (5.7%) | 146 (93%) | 157 (100%) |
| Total | 2 (1%) | 9 (4.4%) | 193 (94.6%) | 204 (100%) |
| Blood transfusion | | | | |
| Yes | 0 (0%) | 0 (0%) | 21 (100%) | 21 (100%) |
| No | 2 (1.1%) | 9 (4.9%) | 172 (94%) | 183 (100%) |
| Total | 2 (1%) | 9 (4.4%) | 193 (94.6%) | 204 (100%) |
| Familial hepatitis | | | | |
| Yes | 0 (0%) | 0 (0%) | 16 (100%) | 16 (100%) |
| No | 2 (1.1%) | 9 (4.8%) | 177 (94.1%) | 188 (100%) |
| Total | 2 (1%) | 9 (4.4%) | 193 (94.6%) | 204 (100%) |

HBcAb: hepatitis B core antibody; HBV: hepatitis B virus.

**TABLE 4.** Distribution pattern of HBV positive and negative patients based on biochemical parameters

| Patients | ALT | | AST | | Total Bilirubin | | Direct Bilirubin | |
|---|---|---|---|---|---|---|---|---|
| | Normal | Ab normal | Normal | Ab normal | Normal | Ab normal | Normal | Ab normal |
| HBcAb positive | | | | | | | | |
| HBV DNA positive | 9 (5.2%) | 0 (0%) | 9 (5.9%) | 0 (0%) | 9 (4.9%) | 0 (0%) | 9 (5%) | 0 (0%) |
| HBV DNA negative | 2 (1.2%) | 0 (0%) | 2 (1.3%) | 0 (0%) | 2 (1%) | 0 (0%) | 2 (1.1%) | 0 (0%) |
| HBcAb negative | 162 (93.6%) | 31 (100%) | 141 (92.8%) | 52 (100%) | 174 (94.1%) | 19 (100%) | 170 (93.9%) | 23 (100%) |
| Total | 173 (100%) | 31 (100%) | 152 (100%) | 52 (100%) | 185 (100%) | 19 (100%) | 181 (100%) | 23 (100%) |

HBV: hepatitis B virus; ALT: alanine transaminase; AST: aspartate transaminase; Ab: antibody; HBcAb: hepatitis B core antibody.

## DISCUSSION

Any immune system disorder, caused by chemotherapy or immunosuppressive agents, may amplify the hazard of HBV reactivation. In the OBI, HBV reactivation may be stimulated by the treatment process of cancers and autoimmune disorders[23,38]. Losing occult HBV infection in cancer individuals, who are planned for chemotherapy, could be harmful. In fact, some of them might develop HBV reactivation, which may result in serious hepatitis and also, in acute hepatic failure with greater mortality. Most of them may turn into chronic carriers of HBV. It could possibly disrupt or delay chemotherapy, as a consequence of hepatitis with decreased chances of survival[20]. Therefore, the aim of this study was set to evaluate the prevalence of OBI, among hepatitis B surface antigen-negative patients with hematologic and solid cancer, prior to receiving chemotherapy.

This study was carried out in the Yazd city of Iran and a large number of cancer patients were screened by using three HBV serum markers; i.e., HBsAg, HBc antibody, and HBV DNA. The prevalence of occult B infection in this study was 9 (4.4%), which is higher than some studies[9,33]; however, it should be stated that the results of some other researches showed a higher prevalence of OBI[8]. Sodhi et al.[34] estimated that OBI incidence among 244 HBsAg-negative cancer patients before receiving chemotherapy was 1.9% (13 out of 690). All these 13 patients were seropositive for anti-HBc antibody. In another study by Cheung and his colleagues[8], where 47 lymphoma patients were studied, 10 out of 47 (21%) had OBI.

In the present study, occult HBV infection was present in 4.4% of cancer patients. In addition, it was higher in hematologic cancers (4.8%) compared to solid cancers (4.3%). This finding is compatible with the study performed by Sodhi et al.[34], where they reported that the incidence of OBI in hematologic and solid cancer patients was 3.6% and 1.4%, respectively. The excessive rates of HBV reactivation were observed in HBV-positive patients undergoing hematopoietic stem-cell transplantation and also, those being treated for hematologic cancers. It should be stated that the risk of HBV reactivation is much less clear in solid tumors compared to patients with hematologic cancers[19,20].

The reasons behind the differences of various investigations for the occurrence of OBI still need to be elucidated. However, immunosuppressive conditions, geographical variations in HBV prevalence, population characteristics, study volume, HBV genotypes, unclear definition of OBI and also, the differences in the sensitivity of the techniques utilized for the diagnosis of the HBV DNA, such as the PCR primer selection methods, might be the reason for these distinctions[35].

In this study, cancer patients with occult HBV infection were with normal ALT, AST, and total and direct bilirubin levels. In the present paper, similar to the earlier documents claimed by other researchers, no relationship was spotted between OBI and the severity of liver disease[10,16]. But some other studies concluded that serious damages are more typical in chronic hepatitis C patients with positive results of the OBI test, compared to those with HCV infection alone[26,29]. Chen et al. disclosed that patients with both OBI and HCV infection had lower ALT ranges[7].

In this investigation, 157 (77%) patients did not receive HBV vaccination before the study. Twenty-one (10%) patients had history of blood transfusion and 16 (8%) patients had history of familial hepatitis. No significant relationship was observed between history of vaccination, blood transfusion and familial hepatitis, and OBI rate ($P$>0.05).

Occult HBV infection can be carried through blood transfusion in cancer patients, except if the transfused blood is analyzed for anti-HB core antibody and HBV DNA[12,34]. Occult HBV infection is known in many countries as the largest cause of transfusion-transmitted HBV infection[4,32]. In spite of the global HBV vaccination program, hepatitis B is still problematic in blood products. Depending on the point that OBI may be regarded as a crucial risk factor for HBV transmission in blood recipients, several researchers have evaluated the prevalence of OBI in blood donors and have also assessed the hazard of OBI transmission through blood and blood products[14].

It should be mentioned that occult HBV patients may develop HBsAg seroreversion, with subsequent HBV reactivation after chemotherapy, particularly in the cases of serious immunosuppression, such as patients of hematopoietic stem-cell transplantation and also, those getting rituximab-based chemotherapy. HBV reactivation following the chemotherapy

results in enhanced morbidity and mortality. Acute hepatitis in these patients creates a delay in the chemotherapy process along with increased chances of relapse. Some patients might experience liver failure and death. Most of these patients are remained in a persistent carrier condition and might cultivate chronic liver disorders, accompanied with its antecedent additional complications[14,18,27].

## CONCLUSION

Patients with occult HBV infections, who receive anticancer chemotherapy, are at risk of HBV reactivation during and after the end of chemotherapy. This study showed that OBI testing needs to be exhaustively performed for cancer patients before getting chemotherapy by estimating their HBV DNA level. Although it might not be economical at this stage, the advantage of estimating HBV DNA prevails over the cost issues.

As a universal policy in many countries, it has been recommended to screen the patients with HBsAg and HBcAb, before the chemotherapy[11]. The outcome of the present study, once again, reinforced the significance of checking for HBV markers, particularly HBV-DNA, in order to diagnose occult HBV infection and various markers such as HBsAg, anti-HBs, anti-HB core antibodies. The greater occurrence of HBV reactivation following the chemotherapy and its related morbidity and mortality should be remained under observation. The individuals, who have negative markers of HBV infection or low anti-HBsAg titers, require prophylaxis against HBV infection by immunization. In addition, those who are HBV positive, need antiviral medicines in order to avoid HBV reactivation. Finally, future studies are necessary to understand the cost effectiveness of HBV-DNA approximation as a checking technique for HBV infection in immune compromised individuals, like cancer patients, who have been selected for further chemotherapy.

## Authors' contributions

Baghbanian M: conception and study design, data collection, analysis and/or interpretation of data, final approval. Halvani M: data collection, analysis and/or interpretation of data, approval of the final version of the manuscript. Roghani HS: data collection and statistical analysis. Lotfi MH: statistical analysis. Yazdi MF and Vahedian-Ardakani H: data collection, analysis and/or interpretation of data, final approval.

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**RESUMO** - ***Contexto*** - A infecção oculta da hepatite B caracteriza-se por antígeno de superfície da hepatite B (AgHBs) negativo com vírus detectável da hepatite B (HBV) -DNA, com ou sem anticorpo de núcleo da hepatite B (anti-HBc). A reativação do HBV em indivíduos sob terapia imunossupressora é crítica, originando a infecção oculta pelo VHB. ***Objetivo*** - Este estudo teve como objetivo determinar a prevalência de infecção oculta pelo VHB entre em pacientes com câncer e com antígeno de superfície da hepatite B negativo antes de receber quimioterapia. ***Métodos*** - Soro de 204 pacientes com câncer que foram negativos para AgHBs, foram testados para anticorpos anti-HBc. As amostras que foram negativos para AgHBs, mas positivo para anti-HBc foram também examinadas para HBV-DNA, por reação em cadeia da polimerase. ***Resultados*** - Entre 204 amostras de sangue AgHBs negativas, 11 (5,4%) foram positivos para anticorpos anti-HBc. HBV-DNA foi detectado em 9/11 (81%) das amostras positivas de anti-HBc. Infecção oculta de VHB em câncer hematológico foi maior que em cânceres sólidos, 4,8% e 4,3% respectivamente. Não houve diferença significativa na positividade anti-HBc, com base na vacinação, transfusões de sangue anteriores, história de hepatite familiar ou parâmetros bioquímicos (ALT, AST, total e níveis de bilirrubina total) (*P* & gt; 0,05). ***Conclusão*** - A triagem de infecção oculta por AgHBs, HBV-DNA e anti-anticorpo de núcleo HB deve ser sugerida como uma investigação de rotina em pacientes com câncer antes de receber a quimioterapia.

**DESCRITORES** - Carcinoma hepatocelular. Vírus da hepatite B. DNA viral. Anticorpos anti-hepatite B. Antígenos do núcleo do vírus da hepatite B.

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