Letter to the Editor

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Occult Hepatitis B Reactivation

Okült Hepatit B Reaktivasyonu

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Dear Editor,

In the recent issue of the Viral Hepatitis Journal, we read with interest the article by Uyanıkoglu et al. (1), "Occult Hepatitis B Reactivation After Chemotherapy: A Case Report". In addition to this article, we wanted to emphasize a few additional important points about the subject.

First of all, definition of occult hepatitis B virus (OHB) infection is long-lasting presence of hepatitis B virus (HBV) deoxyribonucleic acid (DNA) in the liver with detectable (usually very low, <200 IU/ml) or undetectable HBV DNA in the serum of individuals testing hepatitis B surface antigen (HBsAg) negative by currently available assays (2). OHB has been reported in several clinical contexts. However, OHB is most commonly associated with "anti-HBc alone" or "isolated anti-HBc positivity", particularly in endemic areas (3). Another situation labelled "false" OHB with serum HBV DNA levels comparable to the different phases of overt HBV infection could be encountered due to infection by HBV variants with mutations in the "a" determinant region producing a modified HBsAg that is not recognized by some or all available assays (2).

It is a general opinion that the molecular basis of OHB is long-term presence of covalently closed circular DNA (cccDNA) in the nucleus of hepatocyte and also, several possibilities like mutations in the HBV genome, coinfection with hepatitit C virus (HCV), human immunodeficiency virus (HIV) or *Schistosoma mansoni*, deamination by apolipoprotein B mRNA editing enzyme catalytic polypeptide (APOBEC), reduction of host immune response, epigenetic changes due to acetylation, phosphorylation or methylation, integration into the host genome, immune complex formation, and HBV infection in peripheral blood mononuclear cells have been hypothesized as the mechanisms of OHB (4).

The clinical significance of OHB remains unclear. However, it is considered that OHB can be a risk factor for transmission of HBV as well as cryptogenic liver disease, reactivation of HBV, hepatocellular carcinoma, in addition, OHB may affect disease progression and treatment response in chronic HCV (2,3,4,5,6).

Although reactivation of HBV in patients with OHB is rarer than in those with HBsAg positivity, there is a higher risk for mortality and morbidity in patients with OHB (3). OHB reactivation can be associated with cancer therapy, autoimmune diseases, HIV infection, organ transplantation, hematological malignancies and use of immunosuppressive drugs or histone deacetylase inhibitors (Table 1) (5). Other risk factors for OHB reactivation include anti-HBs negativity or its reduction in chemotherapy period, HBV genotype B and the presence of the core or precore mutation (6).

The severity and duration of immunosuppression have an important role in triggering reactivation of HBV infection (3). More severe and frequent reactivation has been reported during hematologic diseases, chemotherapy employed in hematologic malignancies, and allogeneic bone marrow or organ transplantation which elicits more severe and prolonged immunosuppression than homologous bone marrow transplantation or solid tumor chemotherapy (3).

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Table 1. Conditions associated with occult hepatitis B reactivation (5)

Clinical conditions	Therapies
Hematological malignancies - Non-Hodgkin lymphoma - Hodgkin lymphoma - Multiple myeloma - Myelo-monoblastic acute leukemia - Chronic lymphocytic leukemia Transplantation - Hematopoietic stem cell transplantation - Liver transplantation - Bone marrow transplantation - Kidney transplantation HIV infection Rheumatoid arthritis Glioblastoma	- ABVD: Adriamycin+Bleomycin+Vinblastine+ Dacarbazine - BEAM: Carmustine+Etoposide+Cytarabine+Melphalan - CHOP: Cyclophosphamide+Adriamycin/Doxorubicin+ Vincristine+ Prednisone - R-CHOP: Rituximab or CHOP - R-FND: Rituximab+Fludarabine+Mitoxantrone+ Dexamethasone - VAD: Vincristine+Adriamycine+Dexamethasone - Temozolomide - Rituximab (anti CD20) - Alemtuzumab (anti CD52) - Adalimumab - Tocilizumab - Abatacept - Infliximab (anti TNF alfa) - Etanercept - Corticosteroids - Methotrexate - Leflunomide - Bucillamin - Valproic acid - Romidepsin

It has also been reported that OHB individuals may frequently change their HBV serological profile if immunocompromised, although only a minority of these cases develop clinically typical acute hepatitis, and there are studies indicating HBsAg re-seroconversion in patients undergoing hematopoietic stem cell transplantation or receiving rituximab-containing chemotherapy (7,8).

All patients receiving immunosuppressive treatment should be tested for HBV serological markers, including anti-HBc especially before starting therapy (2,5,6). Prophylactic antiviral treatment in hemato-oncological patients with possible OHB (isolated anti-HBc positivity) is still controversial. Testing these patients for HBV DNA and treating them as HBsAg-positive subjects when viral DNA is detectable are recommended, whereas when it is undetectable, they should be followed carefully by means of alanine aminotransferase (ALT) and HBV DNA testing up to a year after the end of immunosuppressive treatment. Confirmation of HBV reactivation by HBV DNA (>30 IU/ml) or a highly sensitive HBsAg assay (low limit of detection <0.1 ng/mL) before ALT elevation is required for beginning antiviral therapy (2,5,6,9).

Not only prophylaxis with antiviral agents, but also prior HBV immunization with an optimal anti-HBs response can prevent reactivation of OHB in most of transplant cases with HBsAg negativity and anti-HBc positivity (6,9). There is no necessity for testing HBV DNA before immunosuppressive therapy in patients with serological evidence of natural immunity of HBV due to past infection (anti-HBs >10 IU/ml). In these cases, following carefully by ALT is reasonable and they are not candidates for prophylactic antiviral treatment (6,9).

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