Association of Hepatitis Virus Infection with Acute and Chronic Myeloid Leukemia: a pilot Study

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ABSTRACT

Background: The induction of cancers by exogenous agents, such as chemical, radiation and especially viruses have been an interested area of basic and clinical research. High prevalence of HBV marker has been found in patients with leukemia as compared to the general population.

Methods: Present study was conducted from 1996 to 2010 by comparing prevalence of Hepatitis virus infection among patients with chronic and acute myeloid leukemia with non malignant patients. In this study we used, Cytochemical staining, immunophenotyping, cytogenetic/molecular cytogenetics, Elisa, enzyme immunoassay and Western blot for the investigation of Hepatitis viruses.

Results: Hepatitis B virus was diagnosed in one non malignant control patient (%0.004) and four leukemia patients (%3). This difference was statistically significant (P=0.0047).

Conclusion: In this pilot study, the prevalence of HBV infection was higher in patients with leukemia than in patients as non malignant patients. Our findings are also important as they are among the first to suggest here a potentially significant influence of HBV infection may play a probably major role in the process of myeloid malignant development. However, the numbers of cases are not large enough to draw firm conclusion. Moreover, we suggest that this pilot study, issue warrants further investigation by large consortium project.

Keywords: Leukemia, AML, CML, HBV, Association.

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ORIGINAL ARTICLE
Introduction

Increased prevalence of hepatitis B surface antigen (HBsAg) have been already reported in the serum of patients with leukemia.\textsuperscript{1,2} especially those suffered from acute myeloid leukemia.\textsuperscript{3}

About 15% of human cancers can be attributed to virus infection.\textsuperscript{4} The attachment site of the virus has been identified in the Pre-S1 encoded protein of the virus envelope, the same involved in hepatocyte infection.\textsuperscript{5} Also, HBV encoded a protein (HBX), and this protein is thought to activate cellular signaling pathways, leading to cellular transformation.\textsuperscript{5} Furthermore, the pertinent studies in the field of cellular study, indicating detection of HBV gene products in the endothelial cells of hematopoietic cancers may suggest an important role of HBV in hematopoietic carcinogenesis.\textsuperscript{6} HBV can also infect bone marrow cells and in vitro studies demonstrated a block of hematopoiesis by HBV, supporting clinical observations of isolate cases of aplastic anemia.\textsuperscript{5} Hematopoietic malignancies comprise a drives group of neoplasms with probable different etiologies.\textsuperscript{7} It has already shown that HBV can induce a chronic lymphocytic inflammatory response in the liver.\textsuperscript{8,9}

Variations in the degree of DNA methylation influence the expression of multiple cancer-related genes, thereby altering to cancer progression. In this context, some reports suggested the role of altered DNA methylation of tumor suppressor genes and oncogenes in the pathogenesis of viral hepatitis carcinoma.\textsuperscript{10} Hepatitis B Virus is known to become integrated into the host genome and undergo epigenetic changes along with the host DNA.\textsuperscript{11-12}

The motive of this pilot study was to analyze a frequency of a group of patients with different subtypes of leukemias associated with hepatitis B and C infection.

Materials and Methods

During sixteen years period (1996 -2010) we received Bone Marrow (BM) and Peripheral Blood (PB) specimens from adult patients diagnosed with acute myeloid leukemia (AML) and chronic myeloid leukemia (CML), from the departments of medical Oncology/Hematology of hospitals affiliated to Shahid Beheshti University of Medical Sciences in Tehran, Iran. 136 adult patients (72 males and 64 females) with ages 20 to 78 years at time of diagnosis with leukemias investigated in this study. Selected control group consisted of 265 non-malignant 21-71 years old patients (164 males and 101 females) from other departments including departments of dermatology, general surgery, Gynecology, Internal medicine, Ophthalmology, and Orthopedics. The diagnosis of acute and chronic myeloid leukemia patients was based on characterization of the leukemic cells, obtained from bone marrow and/or peripheral blood, by cytochemical staining, immunophenotyping, cytogenetic and molecular cytogenetic when appropriate. All selected sample treated with cytogenetic technique according to the International System for Chromosomes Nomenclature-ISCN.\textsuperscript{13}

Analysis of HBV-Related Antigen in the Serum

The sera of the patients was stored at -20°C, then thawed and analyzed for HBsAg with an enzyme-linked immunoassay kit (Diapro Laboratory Diagnostics Milano-Italy).

The laboratory results including HBsAg and Anti-HCV antibody by enzyme immunoassay were performed at the time of diagnosis. To have a strong confirmation, all of HBV-Ab and HCV-Ab positive samples were confirmed by western blot and positive tests were considered as hepatitis B infections. Patients who were positive for HBsAg were considered to have chronic hepatitis B virus. Patients with post –transplant lymphoproliferative disorder, human immunodeficiency virus –positive lymphomas, and chronic Epstein –Barr virus infection associated lymphoproliferative disorders were excluded from this study. Statistical analysis was performed by using SPSS (version 16) software.

Results

We initially enrolled 1,124 patients with different types of hematological malignancies, but we selected 136 leukemias cases (Figure 1), and 389 non-malignant controls (selected by random sampling), due to repeated sampling, this corresponds to 265 unique non-malignant control patients (Figure 2).

Sixty two patients had acute myeloid leukemia. A substantial number of CML patients (74 patients) were in
different phases of disease (60 patients in CP, 5 patients in AP, 9 patients in BC).

Serological results for HBsAg were positive for four cases of leukemia patients and were positive in one patient in non-malignant control patients (Figure 3). Table 1 shows that this difference was statistically different (P=0.0047). In this study, we did not find any significant differences in the age distribution of the patients in the two groups (P>0.05).

The induction of cancers by exogenous agents, such as chemical, radiation and especially viruses is an interested area of basic science research and clinical investigation. Prominent researches have already found a high prevalence of HBV marker in patients with leukemia as compared to the general population.14-19 Our findings presented here are in accordance with others findings reported from different countries elsewhere. In contrast, several studies suggest a weak or non-significant association of HBV with myeloid20 and malignant lymphoma, including NK/T-cell lymphoma and Hodgkin lymphoma.3, 7, 21 Further investigation on the effect of HBV on myeloproliferative malignancies is required to resolve these discrepant findings.

Cases of acute myeloid leukemia were more frequently positive for HBV- DNA in bone marrow specimen, in-
icates that the hemopoietic cells are susceptible to be infected by hepatitis B virus. The examination of bone marrow sample of present study also indicates that HBV is associated with chronic and particularly acute myeloid leukemia. However, one study reported that, association of HBV with other subtypes of leukemia is uncertain.  

In the present study, the prevalence of HBV infection was higher in patients with leukemia than in patients of non-malignant control group. This observation can be considered as another piece of evidence in support of association with HBV infection, considering that leukemic patients were not large enough to draw firm conclusions. Therefore, further studies with large populations of leukemic patients are needed to confirm the possibility of such an association.

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**References**


