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Original Article

High prevalence of hepatitis B virus infection in primary central nervous system lymphoma

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Abstract: Primary central nervous system lymphoma (PCNSL) is a rare extranodal form of non-Hodgkin lymphoma (NHL). The present study aimed to investigate the potential association between infection with the Hepatitis B virus (HBV) and PCNSL. The prevalence of HBV infection in 199 patients with PCNSL was compared in our hospital with that of an age-and sex-matched group of patients with other cancers (except liver cancer), and with a national population-based control group. Enzyme-linked immunosorbent assays were used to test blood samples for HBV markers. It was found that the prevalence of HBV infection in PCNSL was 16.1%, which was higher as compared with patients with other non-hematologic cancers and the national population-based control group. In conclusion, the present study demonstrated that PCNSL patients had a higher prevalence of HBV infection and suggested a potential association between infection with HBV and PCNSL.

Keywords: Primary central nervous system lymphoma, non-Hodgkin lymphoma, hepatitis B virus infection

Introduction

Hepatitis B virus (HBV) infection is the most common cause of chronic liver disease worldwide [1]. China is a highly endemic area of HBV infection, with~170 million carriers [2]. It has been well established that HBV is a hepatotropic virus, and several studies have shown that HBV is also a lymphotropic virus [3, 4]. Several case-control studies with large numbers of patients have found a high prevalence of HBV infection in non-Hodgkin lymphoma (NHL), and revealed a causal association between HBV infection and NHL [5-12]. Several studies also reported the presence of HBsAg in lymphoma cells, which suggested that HBV may have an important role in the development of B-cell NHL [13, 14].

Primary central nervous system lymphoma (PCNSL), is a rare variant of extranodal NHL that accounts for ~1% of lymphomas [15, 16]. By definition, PCNSL is an extranodal malignant lymphoma and it arises within the brain, eyes, leptomeninges, or spinal cord in the absence of systemic lymphoma at the time of diagnosis.

The present study aimed to investigate the potential association between HBV infection and PCNSL.

Patients and methods

Patients

The medical records of 199 unselected and consecutive patients with newly-diagnosed PCNSL, who had received histological diagnosis and treatment in Huashan Hospital, Fudan University, China, between January 2001 and December 2012, were retrospectively reviewed. All patients underwent complete standard blood examinations at baseline, including complete blood counts, measures of liver and renal function, for the presence of HBV markers, hepatitis C (anti-HCV) and HIV antibody (anti-HIV). The prevalence of HBV marker-positive patients in the group with PCNSL was compared with two control groups: A control of non-hematologic malignancies other than liver cancer and a national population-based control. All patients with PCNSL and all patients with non-hemato-

Table 1. Comparison of HBsAg-positive status between patients with PCNSL and controls

Group	HBsAg+ (n)	HBsAg- (n)	Prevalence of HBsAg+ (%)	*P* value*
PCNSL	32	167	16.10	-
Age- and sex-matched non-hematologic cancers	31	367	7.80	0.002*
National population-based control	5,887	75,888	7.20	0.000*

PCNSL: Primary central nervous system lymphoma; *Compared with PCNSL group.

Table 2. Comparison of the prevalence of HBV serologic markers between patients with PCNSL and the non-hematologic cancers group

HBV markers	PCNSL group		non-hematologic cancers group		*P* value
	No. of patients	%	No. of patients	%	
HBsAg+	32	16.1	31	7.8	0.002
Anti-HBs+	83	41.7	142	35.6	0.152
HBeAg+	8	4	14	3.5	0.759
Anti-Hbe+	65	32.7	92	23.1	0.012
Anti-HBc+	93	46.7	133	33.4	0.002

logic malignancies had histologically confirmed diagnosis. All patients were newly-diagnosed and had never been treated with cytotoxic agents.

The PCNSL group included 199 patients, of which 126 patients (63.3%) were male and 73 patients (36.7%) were female. The median age of patients with PCNSL was 55 years (ranging from 18 to 78 years). A total of 197 patients (99.0%) were diagnosed with B-cell NHL and only two patients with T-cell subtype NHL. The non-hematologic malignancies control group consisted of 398 randomly-selected patients (1:2 age- and sex-matched with PCNSL) with non-hematologic malignant tumors, excluding liver cancer due to the known association of liver cancer with hepatitis virus infection. The data on HBV prevalence of the healthy control group was cited from a national cross-sectional study of 81,775 Chinese persons (42,880 females and 38,895 males) aged 1-59 years with weighted HBV prevalence of 7.2% (5,887/81,775), who participated in the National Healthy Survey in 2006 [17].

Serologic Assays for HBV infection

Enzyme-linked immunosorbent assays were used to test serum samples from the PCNSL group and the group of non-hematologic malignancies for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), hepatitis B e antigen (HBeAg), hepatitis B e antibody (anti-HBe), and hepatitis B core antibody (anti-HBc). The same samples were additionally tested for HIV antibody, anti-HCV and used to examine liver function. These assays were conducted in the Central Laboratory of Huashan Hospital, which was accredited by the College of American Pathologists.

Statistics

All data were analyzed using SAS version 8.01. Intergroup comparisons of categorical data were analyzed using Chi-square analysis and differences were interpreted as statistically significant when $P<0.05$.

Results

All 199 patients with PCNSL and all patients with other tumors were HIV-negative. Only one patient with PCNSL and two patients with other cancers were HCV-positive. Of the 199 patients with PCNSL, 32 cases (16.1%) were HBsAg positive. The HBsAg-positive fraction was much higher, as compared with that in the non-hematologic tumor control group (16.1% vs 7.8%, P=0.002) and the healthy control group (16.1% vs 7.2%, P=0.000) (**Table 1**).

Results for the other HBV markers are shown in **Table 2**. The data revealed that patients with PCNSL had a significantly higher incidence of positive test results for HBsAg, HBeAg and anti-HBcAb.

Subsequent investigations further analyzed the co-expression of HBV markers in the PCNSL group and non-hematologic malignancies control group. A combination of the three markers, HBsAg, anti-HBc and anti-HBs, were used to allow for the classification of patients into the following groups: Positive HBsAg, positive HBeAg and positive anti-HBc; positive HBsAg, positive anti-HBe, and positive anti-HBc; nega-

Table 3. Comparison of the prevalence of grouped HBV serologic markers between patients with PCNSL and the non-hematologic cancers group

	PCNSL group		non-hematologic cancers group		*P* value
	No. of patients	%	No. of patients	%	
HBsAg+, HBeAg+, and anti-HBc+	8	4	9	2.2	0.219
HBsAg+, anti-Hbe+, and anti-HBc+	24	12.10%	22	5.8	0.004
HBsAg-, anti-HBsAg+, and anti-HBc-	33	16.6	73	18.3	0.906
HBsAg-, anti-HBsAg+, and anti-HBc+	48	24.1	69	17.3	0.004

tive HBsAg, positive anti-HBsAg and positive anti-HBc positive; nagetive HBsAg, positive anti-HBsAg and nagetive anti-HBc. The results are shown in **Table 3**.

Upon the confirmation of a positive diagnosis of PCNSL, and prior to the initiation of chemotherapy, all patients with PCNSL underwent blood examinations to assess liver function, including alanine transaminase (ALT), aspartate aminotransferase (AST), serum bilirubin (SB). According to the WHO NCI-CTC v3.0 toxicity criteria, values of ALT, AST, and SB exceeding 1.25 times the upper limit of normal are considered to indicate that liver function is impaired. As shown in **Table 4**, the proportion of patients with PCNSL who had impaired liver function was greater for HBsAg positive cases than HBsAg negative cases (Odds Ratio (OR): 7.785, 95% Confidence Interval (CI): 3.31-18.33).

Discussion

The etiology of NHL is unknown, although genetic, environmental, and infectious agents have been implicated. The association between viruses and lymphomas has long been recognized, although the precise mechanisms behind this association are unclear.

Chronic HBV infection is one of the most serious viral infections and is a major risk factor for death from liver cirrhosis and liver cancer. The liver is the main site of HBV replication although extrahepatic organs, such as the lymphoid system, are an important reservoir of the virus [3, 4, 14]. Recent studies confirm that HBV is lymphotropic, and is able to infect and replicate in human lymphocytes and monocytes [3, 4]. One study found that two HBV-associated proteins (HBsAg and hepatitis B core antigen) could be detected in B-cell NHL lymphocytes and endothelial cells of primary tumor tissue from patients with NHL and raising the possibility that B-cell lymphoma and chronic HBV infection in lymph nodes could be linked [14]. Several case-control studies with large numbers of NHL patients, and one meta-analysis that included 12 studies, have shown that the prevalence of HBV is higher in patients with NHL than in the general population or in patients with other solid tumors [11]. Two cohort studies have shown that HBV infection increased the risk of development of NHL [18, 19]. China is one of the areas where HBV is most highly endemic and has ~170 million chronic carriers, of whom ~10% progress to chronic hepatitis. Two studies from China have demonstrated that the prevalence of HBV infection is higher in NHL than in the general population or in patients with other non-hematologic malignant tumors [20, 21]. With regards to NHL subtypes, the association between HBV infection and B-cell NHL has been confirmed, but an association between HBV infection and T-cell NHL has not been found in the majority of studies.

PCNSL is an aggressive and uncommon lymphoma involving the central nervous system (CNS). PCNSL can cause various neurological symptoms and signs and has poor prognosis. PCNSL accounts for 2.4% of primary brain tumors in the United States [14]. Little is known about the tumorigenesis of PCNSL, however, the major risk factor for the development of PCNSL is immunodeficiency. There was nearly a 3-fold increase in the incidence of PCNSL between 1973 and 1984. Infection with human immunodeficiency virus (HIV), which increases the risk of PCNSL by 3,600-fold, as compared with the general population, largely accounted for this increased incidence [14]. HIV seems to be one potential cause of PCNSL. In recent years, the incidence of PCNSL has stabilized. The cause of PCNSL in immune-competent patients is unclear.

One of the characteristics of PCNSL is the histological homogeneity of the tumor. More than

Table 4. The Comparison of liver function between HBaAg+ PCNSL and HBsAg- PCNSL Group

	abnormal liver function	normal liver function
HBsAg+ PCNSL	15	17
HBsAg- PCNSL	17	150

95% of PCNSL tumors are of B-cell origin. In systemic NHL, there is a confirmed association between HBV infection and NHL (especially B-cell NHL). The CNS is an immune-privileged site, thus PCNSL is an immune-privileged site-associated lymphoma, which is one of the distinct characteristics of PCNSL different from systemic NHL. It is therefore worth further investigation to determine whether there is correlation between immune-privileged site-associated lymphoma with HBV infection.

We searched the PUBMED database and found no previous study focusing on a possible association between PCNSL and HBV infection or on the prevalence of HBV in patients with PCNSL. This may be due to the rarity of PCNSL. So, maybe our report is the first report indicating the prevalence of HBV infection is higher in PCNSL than in the general population or in patients with other non-hematologic malignant tumors.

In the present case-control study, it was found that the prevalence of HBV infection and of carrier status were significantly higher in patients with PCNSL than for age- and sex-matched patients with solid tumors (other than liver cancer) or than the general population of China. This finding suggests a possible role for HBV infection in the development of PCNSL. It is therefore hypothesized that immunodeficiency, which predisposes patients with PCNSL to chronic HBV infection, may also allow lymphomagenesis in PCNSL. This is similar to the role of HBV in systemic NHL. HBV integrating in the host genome and chronic stimulation may be possible etiopathogenic mechanisms. Nevertheless, the precise role of HBV in the pathogenesis of HIV-negative PCNSL remains unclear. Some studies have suggested that HBV not only is hepatotropic but also is lymphotropic and may participate in the development of malignant lymphoproliferative disorders.

The present study showed that the majority of clinical characteristics of patients with PCNSL were similar between HBV-positive and HBV-negative subgroups, except for the percentage of patients with abnormal liver function. PCNSL typically affects elderly patients (median age is over 60 years old) [16, 22], for whom chemotherapy, based on high-dose methotrexate (HD-MTX), and whole brain radiotherapy as the standard treatment to PCNSL is a particular burden. For elderly patients, poor compensation of liver and kidney function, plus the liver toxicity of drugs, may mean that patients with PCNSL and with HBV comorbidity are prone to developing liver damage, and that viral replication may increase during PCNSL therapy. The data from the present study therefore suggests that every patient with PCNSL should undergo screening for serum HBV markers prior to initiation of therapy, and should encourage physicians to monitor liver function during therapy more attentively in these patients. Several reports have focused on the potential relation of HBV status and anti-HBV treatment with prognosis of lymphoma [23, 24]. The prognostic significance of HBV infection in patients with PCNSL should be studied in future.

There were only two patients with T-cell PCNSL in the present study and their HBV markers were all negative. With so few patients in this subgroup the correlation between HBV infection with NHL of B-cell or T-cell subtype can't be compared. Another limitation of the present study is that the time point for onset of HBV infection was not available, so the association between duration of HBV infection and time to lymphoma development could not be analyzed.

In conclusion, there is a higher incidence of HBV infection in patients with PCNSL than other non-hematologic or hepatic malignancy, and that there is high risk of liver function impairment in HBsAg-positive patients with PCNSL.

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Disclosure of conflict of interest

None.

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