RESEARCH ARTICLE

Clinical Analysis of Stages of HBV Infection in 100 Cases of Lymphoma

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Abstract

Objective: HBV infection may cause damage to the immune system and induce lymphomas as a result. Some scholars have indicated that HBsAg(+) reflecting HBV infection may have a relationship with lymphoma development. This study was designed to find out the specific stage of HBV infection which may be related to lymphoma. Methods: HBV serum markers, including HBsAg, HBsAb, HBeAg, HBeAb, HBcAb were tested among 100 lymphoma patients and 100 other patients who were diagnosed with non-lymphoma diseases in the First Hospital of Jilin University from 2010.1.1 to 2012.12.31. Three subgroups were established depending on different combinations of HBV serum markers. Subgroup 1 was HBsAg(+) representing the early stage of HBV infection. Subgroup 2 was HbsAb(+) representing convalescence and Subgroup 3 was "HbsAg and HbsAb negative combined with other positive markers" representing the intermediate stage of HBV infection. Chi square tests were used to compare the rates of three subgroups in lymphoma and control groups. Results: The rates of Subgroup were 13% and 5% respectively, an association between HBsAg and lymphoma being found ($P<0.05$). There was no difference between rate of Subgroup 2 of lymphoma group (15%) and that of control group (16%). In lymphoma group and control group , the rate of Subgroup 3 was different (12% vs 4%). This evidence was not specific to T cell lymphoma, B cell lymphoma or Hodgkin's lymphoma. Conclusions: Among serum markers of HBV, the combination of serum markers representing the early stage and intermediate stage of HBV infection have a relationship with lymphoma. Convalescence from HBV infection appears to have no relationship with lymphoma.

Keywords: Lymphoma - hepatitis B virus - serum markers

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Introduction

There is an increasing occurrence of lymphoma, which derived from lympho-hamotolage system (Wang, 2006; Shankland et al., 2012). At least 3.4000 patients' death was caused by lymphoma every year in the world, and this number is increasing rapidly (Alexander et al., 2007). Several virals have been identified as risk factors of lymphoma, such as EBV, HCV and HIV (Mele et al., 2003; Thorley-Lawson et al., 2008; Kathryn et al .,2010). The occurrence of HBV infection is prevalence in China. Some study identified that the hepatitis B virus (HBV) may affect the immune system of humans which may induce lymphocyte clonal proliferation. Since 1999, some scholars have questioned whether HBV regulates the gene of lymphoma generation leading to lymphoma (Cucuianu et al., 1999). Though many case-control studys and meta-analysis, they found lymphoma patients' HBsAg positive rate was higher (Wang et al., 2007; Ulcickas et al., 2007; Chen et al., 2008; Nath et al., 2010; Kim et al., 2011; Paolo et al., 2012), which indicate that the HBV infection may be relate to lymphoma. In 2010, a large cohort study published in Korea (Eric A et al., 2010) found an increased risk of NHL in HBsAg positive participants after a 14 years follow-up. However, the relationship between HBV infection and lymphoma is still in a conflicting state (Kang et al., 2011). While the process of HBV infection complex, including early stage, intermediate stage and convalescence. Different combinations of HBV serum markers signify different stages of HBV infection (Rehermann et al., 2005; Jay, 2009), few researchers pay close attention to the role of combined HBV serum markers (Fabrizio et al., 2012). Thus, in this study, we use different combination of HBV serum markers to study which stages of HBV infection may be relate to lymphoma .

Materials and Methods

Patient

All participants in this study live in Jilin Province, China, and are all diagnosed in the First Hospital of Jilin university, Changchun, from 2010.1.1 to 2012.12.31. Two groups were founded for this research. (1) The lymphoma group:100 lymphoma patients who were all diagnosed with histological biopsy and immunophynotyping

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following World Health Organization Classification of Tumors and the Diagnostic Criteria (Elaine Sarkin Jaffe., 2008). (2) The control group: 100 patients who are diagnosed non-lymphoma diseases. This patients were chosen randomly from patients' database in the first hospital of JiLin university. All participants agreed to answer a questionnaire for data collecting . Data collecting included age, gender, educational level, history of smoking and alcohol intake, the incidence of tumors within the family. After completing the questionnaire, all participants were accepted for the HBV, HCV and HIV serum antigen tests.

HBV serum markers assay

The HBV markers of all patients were detected by ELISA for HBsAg, HBsAb, HBeAg, HBeAb and HBcAb before their therapy .

Relying on the significance of the data,serum markers of HBV, three subgroup were established . (1) HBsAg(+) was studied for Subgroup 1,which represent the early stage of HBV infection. (2) HBsAb (+) combining with HBeAb(+) or HBcAb (+) was studied for Subgroup 2, which represent the convalescence from HBV infection. (3) In both HBsAb and HBsAg negative cases, HBeAb(+) or HBcAb(+) was analyzed for Subgroup 3, which represent the intermediate of HBV infection.

Table 1. Characteristics of the Study Population

Characteristic	Lymphoma group (n=100)	Observation group (n=100)	*P* value
Media Age	50.1 + 16.5	53.2+14.5	0.000
Gender			
(1) Male	67(68%)	60(60%)	0.305
(2) Female	33(33%)	40(40%)	
Education:			
(1)High school or less	45 (45%)	53(53%)	0.287
(2)Some college or college grad	54(53%)	47(47%)	
Current Smoker	29 (29%)	30(30%)	0.877
Alcohol Consumption	18(18%)	16(16%)	0.703

Analysis method

Case-control study was used. The positive ratios of Subgroup 1, Subgroup 2 and Subgroup 3 in lymphoma group and control group were compared using Chi-square test. Analysis was performed using SPSS 19. *P* value<.05 was considered significant difference.

Results

Basic characters of participants

The basic characters of participants was shown in Table 1. The media age, gender distribution, education level, tobacco and alcohol consumption are nearly the same between lymphoma group and control group. All patients' HCV and HIV results were negative, and they had no family history of cancer. All patients had no contact with Formaldehyde which may induce malignant carcinoma. Positive rates of HBV serum markers between lymphoma and control groups are shown in Table 2.

HBsAg(+)

The HBV serum markers of 13 patients in lymphoma group and 5 patients in control group were HBsAg(+). The HBsAg-positive rates (Subgroup 1) of lymphoma group and control group were 13.0% and 5% respectively. The HBsAg(+) rate of lymphoma group was significantly higher than the rate of control group (p=0.048).

HbsAb(+)

The number of HBsAb(+) in lymphoma group was

Table 2. Contrast the Positive Rate of HBV serum Markers Between Cases and Controls

Characteristic	Lymphoma group (n=100)	Observation group (n=100)	*P* value
HbsAg positive (Subgroup 1)	13(13%)	5(5%)	0.048*
HbsAb positive (Subgroup 2)	15(15%)	16(16%)	0.577
HbeAb or HbcAb positive; HbsAg and HbsAb negative (Subgroup 3)	12(12%)	4(4%)	0.037*

Table 3. Contrast the Positive Rate of HBV Serum Markers Between Cases and Controls by Socio-demographic Characteristic

Characteristic	Numbers of HBsAg positive(%)/HBsAb positive(%)/HbeAb or HbcAb positive; HbsAg and HbsAb negative(%) and P value	
Charactor (numbers)	Lymphoma group (n=100)	Observation group (n=100)
Age (lymphoma/controls)		
<40 (26/18)	2(7.7%)/3(11.5%)/4(15.3%) P value:0.228/0.143/0.081	0/0/0
40-60 (47/52)	5(11%)/12(25.5%)/4(8.5%) P value: 0.611/0.951/0.135	4(7.7%)/13(25.0%)/1(1.9%)
>60 (27/30)	6(22.2%)/0(0%)/4(14.8%) P value:0.03*/0.091/0.581	1(3.3)/3(10%)/3(10%) 7.7
Gender		
(1) Male (67/60)	9(13.4%)/11(16.4%)/9(14.7%) P value:0.08/0.97/0.029	2(3.3%)/10(16.7%)/4(6.7%)
(2) Female (33/40)	4(12.1%)/4(12.1%)/3(9.0%) P value: 0.167/0.97/0.05*	3(7.5%)/6(15.0%)/0
Education:		
(1)High school or less (45/53)	4(8.8%)/8(17.8%)/6(13.3%) P value:0.809/0.728/0.109	4(7.5%)/9(17.0%)/3(5.7%)
(2)Some college or college grad (55/47)	9(16.3%)/7(12.7%)/6(23.6%) P value: 0.016*/0.751/0.08	1(0.02%)/7(14.8%)/1(16.7%)

Table 4. Contrast the Positive Rate of HBV Serum Markers among B-cell, T-cell and Hodgkin Lymphoma (HL)

	B-cell lymphoma (n=64)	T-cell lymphoma (n=26)	HL (n=10)	*P* value
HbsAg positive	9(14.0%)	4(15.3%)	1(10%)	0.916
HbsAb positive	7(10.9%)	7(26.9%)	1(10%)	0.141
HbeAb or HbcAb positive; HbsAg and HbsAb negative	5(7.8%)	4(15.3%)	3(30%)	0.110

15 and that in control group was 16. The HBsAb(+) rate (Subgroup 2) between lymphoma group and control group was not different (15% vs 16%, p=0.577).

Other serum markers

The rates of "HBsAg-negative, HBsAb-negative with any other positive markers" (Subgroup 3)in lymphoma group and control group were 12% and 4%. The rate of lymphoma group was higher than control group (p=0.037).

Serum markers and basic characters

When age, gender and education level of the diagnosed patients were considered, the HBsAg-positive rate between lymphoma group and control group was different only with patients over 60 years old or patients with high educational level (Table 3). In addition only in female, the different rate of Subgroup 3 between lymphoma group and control group was shown. The HBsAg(+) rates between lymphoma group and control group in male were 13.4% and 3.3%; But in female the HBsAg(+) rates were 12.1% and 7.5%. There may be a difference following increased number of cases.

Serum markers and different types of lymphoma

We compared the rate of Subgroup 1, Subgroup 2 and Subgroup 3 in different types of lymphoma(Table 4). The HbsAg positive rates(Subgroup 1) of T- cell, B-cell and Hodgkin lymphoma were 14%, 15.3% and 10%, respectively. The HBsAb positive rates(Subgroup 2) of T- cell, B-cell and Hodgkin lymphoma were 10.9%, 26.9% and 10%, respectively. The HBsAg and HBsAb negative combined with other markers positive rates (Subgroup 3) of T-cell, B-cell and Hodgkin lymphoma were 7.8%, 15.3% and 30%, respectively. There were no significant differences between the different types of lymphoma.

Discussion

Lymphoma, a kind of malignant carcinoma derived from immune system, has a close relationship with lymphocyte proliferation and differentiation of certain malignant immune cells (Alexander et al., 2007). Currently, the viral etiology of lymphoma was taken seriously. HBV is DNA virus (Tiollais et al., 1985), it may induce some kind of tumors, such as human hepatic carcinoma(HCC), due to HBV-DNA integrating to hepatic cell group DNA (Zhu et al., 2005). So, whether HBV is able to induce lymphoma, how HBV induce lymphoma? These questions were presented by researchers recently. HBV-induced lymphoma has become a serious problem.

In past decades, researchers began to pay close attention to the relationship between HBV and lymphoma. Sine 2008, many professors from Japan, China, US ,Europe and Korea showed the close relationship between HBV and lymphoma, especially non hodgkin lymphoma (NHL) (Ulcickas et al., 2007; Chen et al., 2008; Kim et al., 2011; Paolo et al., 2012). In our study, the HBsAg-positive rate of lymphoma group was 13%, which was higher than that of control group. Compared with other findings, it may sure that the lymphoma may have a relationship with HBsAg(+). But the mechanism is still conflicting.

The HBsAg(+) signifies that the patients suffer from HBV infection, and their viral replication is active. This status often happens at the early stage of HBV infection. Our data showed that the HBV(+) rate of lymphoma group is obviously higher than that of the control group. There may be a close relationship between lymphoma and the early stage of HBV infection. At the early stage of HBV infection, the cytotoxic lymphocytes (CTLs) could be detected in the peripheral blood (Li et al., 2011), which means the immune response begins to be established against HBV. HBV, as one kind of antigen, may stimulate T, B cells to transform into effective cells against virus, followed by some abnormal immune cell stimulation, which may induce T or B cell lymphoma (Altman et al., 2012) .

HBeAb(+) signifies that in the patient's body, the viral replication reduces while HBV remains infectious. HBcAb(+) may be seen at acute or chronic HBV infection. These positive serum markers' combination in Subgroup 3 signify the intermediated stage of HBV infection. Our study showed that lymphoma patients had a higher rate of "HBeAb positive or HBcAb positive combined with HBsAg and HBsAb negative"(Subgroup 3). This result provided the evidence that not only the early stage of lymphoma, but the intermediate stage also had close relationship with lymphoma. At this stage, the organism has established an effective mechanism against HBV. It was found that the peak level of CTLs often appears with HBeAg, which appears after serum HBsAg and HBV-DNA peak levels (Li et al., 2011). Though the CTL plays a major role in the clearance of virus, the HBV still exists in the body. The immune system and HBV may get a subtle balance for a long time until the convalescence stage.

The HBsAb-positive with HBsAg-negative signifies the last stage of HBV infection. At this stage, the HBV is almost cleared by human immune system. In our study, HBsAb-positive rate in lymphoma group and control group had no significant difference. It meaned that the convalescence from HBV infection had no obvious relationship with lymphoma. The reason may be due to lacking of the course of stimulation which may lead to decrease in chance of lymphoma production.

From these results of our study, it may illustrated that the occurrence of lymphoma may be induced by the chronic conflict between immune system and HBV, but not by the mutation of genes. In patients with HBV infection, the immune response is a strong, multi-specific cellular immune response. HBV may cause lymphocytes to activate. The mechanism of activation of lymphocytes is proved to be similar to that of lymphoma (Michalek et al., 2010; Altman et al., 2012). The HBV

may stimulate the Lymphohematopoietic system continuously, and eventually lead to clonal proliferation of malignant lymphocytes. The hypothesis maybe similar to the conjecture that HCV promotes the development of lymphoma (Quinn et al., 2001). On the other hand, we still do not find any evidence from lymphoma biopsies (Park et al., 2008), so the relationship between HBV and the pathogenesis of lymphoma requires further confirmation.

In conclusion, our study provided an association between HBV serum markers and lymphoma, especially the combination of HBV serum markers which present the early and intermediate stage of HBV infection. This evidence is not specific in any types of lymphoma. These dates suggest that HBV infection may play a potential role in the occurrence of lymphoma. But, it still need more evidence to prove such hypothesis. We recommend regular checkups to detect the existence of lymphoma for the patients with HBsAg, HBeAg, HBeAb or HBcAb positive.

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