LETTER TO THE EDITOR

Prevalence of hepatitis B and hepatitis C viral infections in various subtypes of B-cell non-Hodgkin lymphoma: confirmation of the association with splenic marginal zone lymphoma

Non-Hodgkin lymphoma (NHL) ranked as the sixth most common cancer in 2016. Its incidence has steadily increased in the past decade. Both environmental and genetic factors can promote the development of NHL. It has been hypothesized that chronic antigenic stimulation, especially due to a virus such as the human immunodeficiency virus, Epstein-Barr virus and hepatitis C virus (HCV), plays an important role in the pathogenesis of NHL. Previous data indicated that hepatitis B virus (HBV) infection is associated with B-cell NHL (B-NHL) in HBV-prevalent areas such as Japan and Korea. However, studies that systematically evaluate the prevalence of HBV and HCV infections in each B-NHL subtype are rare. In this study, we aimed to illustrate the distribution of hepatitis virus infection in a large series of B-NHL patients in China, a region in which hepatitis virus infection is prevalent.

In total, 733 newly diagnosed indolent patients and 148 aggressive B-NHL patients with integrated HBV and HCV results were unselectively enrolled in this study. The diagnosis criterion was in accordance with the World Health Organization Classification of Tumors of Hematopoietic and Lymphoid Tissues. The B-NHL subtypes are shown in Table 1. HBs-Ag and anti-HCVAb-positive patients were considered to have HBV and HCV infection, respectively. To compare the hepatitis viral infection data with that of the normal population, we referenced the recent epidemiological investigation of the hepatitis viral infection in China, which enrolled 81,775 residents with HBV and 78,746 residents with HCV.

With regard to HBV infection status, 9.0% of the patients (79/881) were HBs-Ag-positive, which was significantly higher than the proportion in the general population, as shown in Table 1.

Table 1. Prevalence of HBV and HCV infection in patients with different types of B-cell non-Hodgkin lymphoma

| Category | Total (N) | HBs-Ag infection rate | HCV infection rate |
|----------|-----------|------------------------|--------------------|
|          | N (%)     | Unadjusted odds ratio (95% CI) | P value | N (%)     | Unadjusted odds ratio (95% CI) | P value |
| General population | 81,775 | 5,888 | 7.2 | Reference | 316 | 0.40 | Reference |
| General population | 78,746 | | | | | |
| B-NHL patients | 881 | 79 | 9.0 | 1.270 (1.006-1.602) | 0.044 | 16 | 1.8 | 4.606 (2.775-7.645) | 0.000 |
| Indolent B-NHL | 733 | 58 | 7.9 | 1.107 (0.846-1.450) | 0.458 | 14 | 1.9 | 4.848 (2.824-8.322) | 0.000 |
| Aggressive B-NHL | 148 | 21 | 14.2 | 2.131 (1.342-3.384) | 0.001 | 2 | 1.35 | 3.411 (0.841-13.828) | 0.068 |
| According to indolent lymphoma subtype | | | | | |
| SMZL | 48 | 9 | 18.8 | 2.974 (1.440-6.143) | 0.002 | 2 | 4.2 | 10.826 (2.617-44.788) | 0.000 |
| CLL | 279 | 21 | 7.5 | 1.049 (0.672-1.638) | 0.833 | 6 | 2.2 | 5.472 (2.419-12.380) | 0.000 |
| LPL/WM | 119 | 6 | 5.1 | 0.684 (0.301-1.556) | 0.363 | 3 | 2.6 | 6.439 (2.036-20.366) | 0.000 |
| FL | 74 | 6 | 8.1 | 1.137 (0.493-2.621) | 0.763 | 0 | 0 | | 0.586 |
| B-LPDu | 132 | 10 | 7.6 | 1.056 (0.554-2.014) | 0.868 | 1 | 0.76 | 3.411 (0.841-13.828) | 0.068 |
| HCL | 33 | 4 | 12.5 | 1.778 (0.625-5.058) | 0.274 | 1 | 3.0 | 7.781 (1.060-57.116) | 0.017 |
| NMZL | 27 | 3 | 11.1 | 1.611 (0.485-5.352) | 0.432 | 1 | 3.7 | 9.576 (1.296-70.786) | 0.007 |
| MALT | 15 | 0 | 0 | 0.281 | 0 | 0 | 0.806 |
| B-PLL | 6 | 0 | 0 | 0.495 | 0 | 0 | 0.877 |
| According to aggressive lymphoma subtype | | | | | |
| DLBCL | 58 | 12 | 20.7 | 3.362 (1.780-6.350) | 0.000 | 0 | 0 | | 0.629 |
| MCL | 59 | 8 | 13.6 | 2.022 (0.959-4.262) | 0.059 | 2 | 3.5 | 9.054 (2.199-37.279) | 0.000 |
| Burkitt lymphoma | 2 | 0 | 0 | 0.694 | 0 | 0 | 0.929 |
| B-LBL | 14 | 0 | 0 | 0.297 | 0 | 0 | 0.813 |
| Aggressive B-NHL unclassified | 15 | 1 | 6.7 | 0.921 (0.121-7.002) | 0.936 | 0 | 0 | | 0.806 |

Abbreviations: B-LBL, B-cell lymphoblastic lymphoma; B-LPDu, unclassified B-cell chronic lymphoproliferative disorders; B-NHL, B-cell non-Hodgkin Lymphoma; B-PLL, B-cell prolymphocytic leukemia; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; HBV, hepatitis B virus; HCL, hairy cell leukemia; HCV, hepatitis C virus; FL, follicular lymphoma; LPL/WM, lymphoplasmacytic lymphoma/Waldenström macroglobulinemia; MALT, mucosa-associated lymphoma; MCL, mantle cell lymphoma; NMZL, nodal marginal zone lymphoma; SMZL, splenic marginal zone lymphoma. P value comes from comparison with general population; bold indicates significant difference (P < 0.05).
Specifically, a significantly higher prevalence of HBV infection in patients with aggressive B-NHL was observed compared to both the indolent B-NHL group and the general population. The subtype analysis of the aggressive group is shown in Table 1. The presence of HBs-Ag was comparable in the indolent B-NHL and the general population. Unexpectedly, among all the indolent B-NHL subtypes, 9 of the 48 (18.8%) splenic marginal zone lymphoma (SMZL) patients were HBs-Ag-positive. A positive association was observed between SMZL and HBs-Ag seropositivity. Furthermore, compared to other indolent B-NHL subtypes, the SMZL group also had a significantly higher HBs-Ag infection rate (18.8 vs 7.1%, \( P = 0.005 \)).

The prevalence of HCV infection in the subtypes of B-NHL is also shown in Table 1. Compared to the general population, the anti-HCV-Ab-positive rate was significantly higher in the entire B-NHL group and the indolent B-NHL group. Only two mantle cell lymphoma patients had an HCV infection in the aggressive B-NHL. However, HCV infection was universal in the indolent B-NHL group. Remarkably, the SMZL group had the highest HCV infection rate.

This is the first study to evaluate the HBV and HCV infection rate in each subtype of B-NHL systematically in a large series. We found that not only HBV but also HBV seropositivity was associated with some but not all B-NHLs. Due to the geographical and epidemiological variability as well as different lymphoma morbidity, the results varied across areas. However, an increasing number of reports support a variability as well as different lymphoma morbidity, the results varied but not all B-NHLs. Due to the geographical and epidemiological variability as well as different lymphoma morbidity, the results varied but not all B-NHLs. In conclusion, we confirm that hepatitis virus infection differs in B-NHL subtypes. The prevalence rate of both HBV and HCV in SMZL patients was higher than that of the general population and other indolent B-NHL subtypes, suggesting that hepatitis virus infection might play an etiologic role in SMZL pathogenesis.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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