

## Hepatitis Virus Infection and Hodgkin's Lymphoma: A Review of the Literature

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**Hepatitis virus infection is an increasing problem, with millions of people all over the world being infected. It is accepted as a significant public health problem with several life altering complications, especially hepatocellular carcinoma. Hepatitis viruses especially for hepatitis C and hepatitis G have been mentioned as a risk factor for development of Hodgkin's lymphoma. In this work, the author summarized the evidence on the correlation between Hodgkin's lymphoma and hepatitis virus infection focusing on hepatitis C and hepatitis G. Conclusively, hepatitis C and hepatitis G virus can contribute high risk for development of Hodgkin's lymphoma.**

**Keywords:** Hodgkin's Lymphoma, Hepatitis C, Hepatitis G

### Introduction

Keresztes *et al.* showed that numerous observations implied that the pathogenesis of malignant lymphomas was multifactorial and that viruses probably played an important etiologic role<sup>(1)</sup>. Lymphoma is a common hematological malignancy. Fisher and colleague said that several pathogens have been linked to the risk of lymphoma, including Epstein-Barr virus, human immunodeficiency virus, hepatitis virus, and simian virus 40<sup>(2)</sup>. Hepatitis viruses especially for hepatitis C<sup>(3, 4)</sup> and hepatitis G<sup>(3)</sup> have been mentioned as a risk factor for development of Hodgkin's lymphoma. In this work, the author summarized the evidence on the correlation between Hodgkin's lymphoma and hepatitis virus infection focusing on hepatitis C and hepatitis G.

### Hepatitis C Infection and Hodgkin's Lymphoma

There are many studies on the carcinogenesis role of hepatitis C virus (HCV). Major topics of the

study are the biological functions of HCV proteins and the interaction between HCV proteins and cellular proteins<sup>(5)</sup>. HCV infection has shown to be strongly linked to the development of hepatocellular carcinoma (HCC) in epidemiological studies<sup>(6)</sup>. Unlike other human oncogenic viruses, HCV is a typical RNA virus, and thus there is no integration of the viral genome or a piece of the genome into host chromosomes<sup>(6)</sup>. Moreover, trans-acting transcriptional factors, which are coded by other human oncogenic viruses and required primarily for virus replication and often involved in cell immortalization, may not be coded by HCV<sup>(6)</sup>.

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Hausfater *et al.* mentioned that the finding of HCV binding on CD81, a surface-expressed protein present on lymphocyte membrane, enhanced the putative role of HCV in lymphoma genesis <sup>(7)</sup>. Observations made with isolated HCV antigens and/or with HCV subgenomic replicon systems demonstrated that the products encoded in the HCV genome interfere with and disturb intracellular signal transduction, often by phosphorylation of cellular proteins <sup>(8)</sup>. Moreover, some of the HCV- encoded proteins seem to serve as substrates for host cell protein kinases <sup>(8)</sup>. The identification of these small polypeptide elements and the subsequent development of strategies to inhibit protein-protein interactions involving them may be the first step towards reducing the chronicity and/or of the carcinogenicity of the virus <sup>(8)</sup>.

Considering the lymphoma genesis due to HCV infection, Quinn *et al.* proposed that some HCV-associated lymphomas originated from B cells that were initially activated by the HCV-E2 protein and might explain the association between HCV infection and some B-cell lymphoproliferative disorders <sup>(9)</sup>. Indeed, Montella *et al.* said that HCV was an RNA virus that could not be integrated with the host genome, however, exerted its oncogenetic potential indirectly by contributing to the modulator effects of the host immune system, probably through a capacity to elude the immune system <sup>(10)</sup>. Fiorilli *et al.* said that molecular data indicated a close relationship between HCV-associated B-non Hodgkin's lymphoma and type II mixed cryoglobulinemia <sup>(11)</sup>. They noted that the latter disorder appeared to reflect the benign monoclonal proliferation of B cells expressing a specific cross-reactive idiotype that might recognize an antigen of HCV, perhaps the E2 protein then genetic abnormalities occurring during this phase of antigen-induced clonal expansion might drive the neoplastic transformation into low- or high-grade lymphoma <sup>(11)</sup>.

Concerning the relationship between HCV infection and Hodgkin's lymphoma, there are only a few reports. Keresztes *et al.* proposed that HCV positivity in patients with Hodgkin's disease differs significantly (about 1.5 times) from that in blood donors <sup>(1)</sup>. They also noted that there was no significant difference between hepatitis positive and negative patients concerning mean age at the time of diagnosis, sex, disease stage, histology type, treatment, risk factors in the history of infection, and liver enzymes <sup>(1)</sup>. According to their report, 9% of the patients with Hodgkin's lymphoma were anti-HCV seropositive <sup>(1)</sup>. Recently, Yenice *et al.* noted that HCV might play a role in the development of B-cell

non-Hodgkin's lymphoma, but not in Hodgkin's lymphoma <sup>(12)</sup>.

Recently, Wiwanitkit performed a metaanalysis to perform an appraisal on the seroprevalence of HCV among patients with Hodgkin's lymphoma comparing with healthy control subjects <sup>(13)</sup>. According to the literature review, 3 reports were recruited. According to the metaanalysis, 184 cases and 904 healthy subjects were investigated for HCV seroprevalence. The overall anti-HCV seropositivity rate in the patients (3/184) and healthy subjects (6/904) was 1.6% and 0.7%, respectively. The odds ratio was 2.5 <sup>(13)</sup>. According to this study, it could be seen that anti-HCV seropositivity is a risk factor for Hodgkin's lymphoma <sup>(13)</sup>.

## Hepatitis G Infection and Hodgkin's Lymphoma

Presently, many new hepatitis viruses are identified and proposed for their possible role in pathogenesis of many disorders. Hepatitis G virus (HGV) is an example of a newly detected hepatitis virus <sup>(14, 15)</sup>. Only a few data are available concerning the newly discovered HGV and extrahepatic manifestations such as hematological malignancies <sup>(16)</sup>, but HCV and HGV most probably belong to the same family of Flavivirus, similar correlation to the development of lymphoma could be expected <sup>(16, 17)</sup>. The correlation between this virus and development of Hodgkin's lymphoma is of interest. Here, the author performs an appraisal on the prevalence of HGV-RNA among patients with Hodgkin's lymphoma comparing with healthy control subjects. Risk analysis was performed. The author hypothesized that the HGV-RNA positivity might be an important risk factor for Hodgkin's lymphoma.

According to the literature review, at least 3 reports <sup>(1, 16, 17)</sup> covering 282 cases of Hodgkin's lymphoma can be seen. The overall prevalence of HGV-RNA positivity is 11.7% (33/282). Of the 3 reports, only 2 reports have complete data on the prevalence in both patients with Hodgkin's lymphoma and healthy control subjects and are used for further metaanalysis study. According to the metaanalysis, 171 cases and 181 healthy subjects were investigated for HGV-RNA. The overall antibody positive rate in the patients and healthy subjects were 14.0% (24/171) and 1.1% (2/181), respectively. The odds ratio was 16.9%. It could be seen that serum HGV-RNA positivity is a very high risk factor for Hodgkin's lymphoma. This data support the report of De Renzo *et al.* that HGV infection might play a role in lymphoma genesis <sup>(16)</sup>.

## Hepatitis TT Infection and Hodgkin's Lymphoma

The information on the correlation between this blood borne virus and Hodgkin's lymphoma is limited. There is only one report on this topic. Garbuglia *et al.* reported high prevalence of hepatitis TT virus DNA in lymphocytes circulating in the lymph nodes of both B-cell lymphomas and Hodgkin's lymphoma <sup>(18)</sup>. They suggested an implication of hepatitis TT virus infection in the development of these lymphoproliferative disorders <sup>(18)</sup>.

## Conclusions

There is scientific evidence that hepatitis C and hepatitis G virus can contribute to the high risk for development of Hodgkin's lymphoma.

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