

## Hepatitis C infection and lymphoproliferative disease: Accidental comorbidities?

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Science, Google Scholar, and the Cochrane Database of Systematic Reviews, with search terms broadly defined to capture discussions of HCV and its relationship with NHL and/or lymphoproliferative diseases. References were screened to further identify relevant studies and literature in the basic sciences. A total of 62 reports discussing the relationship between HCV, NHL, and lymphoproliferative diseases were identified. Epidemiological studies suggest that at least a portion of NHL may be etiologically attributable to HCV, particularly in areas with high HCV prevalence. Studies that showed a lack of association between HCV infection and lymphoma may have been influenced by small sample size, short follow-up periods, and database limitations. The association appears strongest with the B-cell lymphomas relative to other lymphoproliferative diseases. Mechanisms by which chronic HCV infection promotes lymphoproliferative disease remains unclear. Lymphomagenesis is a multifactorial process involving genetic, environmental, and infectious factors. HCV most probably have a role in the lymphomagenesis but further study to clarify the association and underlying mechanisms is warranted.

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### Abstract

Chronic hepatitis C virus (HCV) infection has been associated with liver cancer and cirrhosis, autoimmune disorders such as thyroiditis and mixed cryoglobulinemia, and alterations in immune function and chronic inflammation, both implicated in B cell lymphoproliferative diseases that may progress to non-Hodgkin lymphoma (NHL). HCV bound to B cell surface receptors can induce lymphoproliferation, leading to DNA mutations and/or lower antigen response thresholds. These findings and epidemiological reports suggest an association between HCV infection and NHL. We performed a systematic review of the literature to clarify this potential relationship. We searched the English-language literature utilizing Medline, Embase, Paper First, Web of

**Key words:** Blood; Hepatitis C infection; Non-Hodgkin's lymphoma; Pathogenesis; Treatment

**Core tip:** This is a review of the literature regarding the relationship between hepatitis C virus and lymphoproliferative disease, an issue with unresolved conclusions until today.

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## INTRODUCTION

Chronic hepatitis C virus (HCV) infection is an insidious form of liver disease that can silently progress to cirrhosis over a period of 10-30 years in 20% of cases. Chronic HCV infection has also been associated with extrahepatic manifestations, including membranoproliferative glomerulonephritis, various autoimmune disorders, and idiopathic pulmonary fibrosis.

HCV is a single, positive-strand RNA hepatotropic virus with marked genetic variability<sup>[1]</sup>. It exhibits lymphotropism, the ability to replicate in peripheral blood mononuclear cells, which may represent the association between HCV infection and the development of lymphoproliferative disorders<sup>[2]</sup>. HCV is a the possible cause of B-cell dysregulation diseases and conditions and B-cell lymphoproliferative disorders that may progress to non-Hodgkin lymphoma (NHL)<sup>[3]</sup>, three and was identified as a principle cause of mixed cryoglobulinemia<sup>[4,5]</sup>.

Infectious agents have been associated with the development of B-cell lymphoma<sup>[1]</sup>, and several studies have suggested that infection with HCV is a risk factor for the development of B-cell NHL<sup>[1-3]</sup>.

Oncogenesis is a multifactorial process in which many viruses, including Epstein-Barr virus, human papilloma virus, and human T cell leukemia/lymphoma virus, play a well-known role. Epidemiological studies have demonstrated an association between HCV infection and NHL<sup>[6-10]</sup>, suggesting that HCV infection plays a role in the development of premalignant and malignant hematologic disorders<sup>[2,6,11,12]</sup>. Other studies have shown that treatment of NHL with antiviral therapy in patients infected with HCV can lead to regression of lymphoproliferative disease<sup>[13,14]</sup>. In contrast, other studies have shown a lack of association between HCV infection and the development of lymphoma<sup>[15,16]</sup>; thus, debate regarding a potential relationship between HCV and NHL continues.

## RESEARCH

We searched the English-language literature utilizing Medline, Embase, Paper First, Web of Science, Google Scholar, and the Cochrane Database of Systematic Reviews, with search terms broadly defined to capture discussions of HCV and its relationship with NHL and/or lymphoproliferative diseases. References were screened to further identify relevant studies and literature in the basic sciences.

### **Findings supporting the association between HCV and NHL**

In one study 3 on HCV-positive patients, 13.7% (32/233) had monoclonal gammopathy compared to an incidence in the general population of 1%. Of the 32 cases, 24 (75%) were benign and were not associated with a malignant disorder; however the other eight (25%) were associated with a malignant lymphoproliferative disorder or plasma cell disorder, and two additional subjects with-

out monoclonal gammopathy were diagnosed as having a malignant lymphoproliferative disease. In this study, the overall prevalence of malignant lymphoproliferative disease/plasma cell disorder in individuals with HCV infection was 4.3%. Monoclonal gammopathy was found in 14% of the patients with chronic HCV infection and was associated with malignant lymphoproliferative disease in more than 25% of such patients.

Another study<sup>[17]</sup> showed that the prevalence of HCV among lymphoproliferative disease patients was 7.8% compared with a prevalence of 1.19% in the group with myeloproliferative and myelodysplastic disorders, and 0.64% in the general population. After subtype analysis, the strongest association between HCV and lymphoproliferative disease was found in patients with diffuse large B-cell lymphoma. The authors proposed that an anti-HCV antibody test should be performed routinely in lymphoma patients.

In another study, HCV prevalence was 17.5% (70/400) in lymphoma patients and 5.6% (22/396) in controls. The highest prevalence rates were found among patients with lymphoplasmacytic lymphoma and marginal zone lymphoma (30% and 26.6%, respectively), both of which are considered indolent types of B-cell NHL. Among the two largest subgroups of B-cell NHL, the HCV prevalence was more elevated among patients with large B-cell lymphoma (19.0%), an aggressive form of B-cell NHL, compared to patients with follicular B-cell NHL (13.9%), an indolent form of lymphoma. This study suggests that the association between B-cell NHL and HCV infection is not genotype-specific because no difference in genotype distribution was found between the control group and the study group<sup>[18]</sup>.

In contrast to the findings described above, several other studies have found that the genotype 2a was more frequent among patients with monoclonal gammopathy than those without<sup>[19,20]</sup>. Furthermore, genotypes 1b and 2a were suggested to be risk factors for the developing lymphoma in HCV patients<sup>[21]</sup>.

Other studies have compared the prevalence of HCV infection among patients with different types of lymphoproliferative disorders, including Hodgkin's disease, acute lymphoblastic leukemia, multiple myeloma, T-cell NHL and B-cell NHL. A total of 537 patients were tested for HCV infection and compared to the general population. Among all lymphoproliferative disorders, the prevalence and the relative risk (RR) of being infected with HCV was increased only in those with B-cell NHL and, specifically, in the subgroup of immunocytomas, whereas the histologic types of other patients were only occasionally associated with HCV infection<sup>[22]</sup>. Likewise, a recent meta-analysis of 15 case control studies and three prospective studies found a higher RR for NHL among HCV-positive individuals and the etiologic fraction of NHL attributable to HCV was more than 10% in areas with high HCV prevalence<sup>[23]</sup>.

Finally, in a seminal study, response to interferon therapy (interferon  $\alpha$  and ribavirin, alone and in combination)

was compared for nine patients having splenic lymphoma with villous lymphocytes and HCV infection versus a control group of six similarly treated patients having splenic lymphoma with villous lymphocyte who tested negative for HCV infection. All nine patients who tested positive for HCV had a remission of their lymphoma after the loss of detectable HCV RNA in the blood, and one patient had a relapse when HCV RNA became detectable again. In contrast, none of the six HCV-negative patients had a response to interferon therapy<sup>[14]</sup>. Similar findings were published in a subsequent study<sup>[24]</sup>. These studies comprise one of the strongest arguments supporting the association of HCV infection with NHL.

### **Mechanism of pathogenesis**

The mechanism by which chronic HCV infection promotes lymphoproliferative disease remains unclear. Some studies have shown that treatment of HCV infection with viral elimination methods reduces the incidence of malignant lymphoma in patients infected with HCV<sup>[14,25-27]</sup>. Over the years, several theories involving different mechanisms have been proposed. One such idea is that hypermutation induced by HCV infection of the immunoglobulin genes in B cells can be the cause of lymphomagenesis<sup>[28,29]</sup>. Another proposed theory is that HCV infection-induced hypermutation causes genetic instability and chromosomal aberrations, possibly resulting in neoplastic transformation<sup>[30]</sup>. Soluble interleukin 2 receptor (sIL-2R) has been shown to take part in some cancers, including T-cell lymphoma, nasopharyngeal carcinoma, lung and breast cancer, epithelial ovarian cancer, renal cell carcinoma, and hepatocellular carcinoma in Egyptian patients<sup>[31-37]</sup>. In splenocytes of HCV transgenic mice that express the full HCV genome in B cells (RzCD19Cre mice), the level of IL-2R was higher than levels in splenocytes derived from mice that express Cre under the transcriptional control of the B lineage-restricted CD19 gene. (CD19Cre mice). Furthermore, serum concentrations of sIL-2R in RzCD19Cre mice that developed B-cell lymphomas were higher. Serum sIL-2R $\alpha$  levels above 1000 pg/mL were highly suggestive for the development of B-cell lymphomas in RzCD19Cre mice<sup>[38]</sup>.

Chronic antigenic stimulation is thought to be important in the pathogenesis of HCV-related B-cell NHL. The immune response that occurs in HCV-positive patients against one HCV antigen, the E2 envelope glycoprotein (E2), suggests that the restricted V gene observed in lymphoproliferative disorders may be linked to this antigen. V-region genes from human anti-E2 antibodies derived from B cells of HCV-infected individuals show a similar V gene bias to that observed in HCV-associated mixed cryoglobulinemia and NHL<sup>[39,40]</sup>. These studies implicate the specific immune response against the E2 antigen in the pathogenesis of B-cell lymphoproliferative diseases and, potentially, in HCV-associated lymphomas. The E2 protein may be the antigen involved in driving B cell proliferation. B cells bind E2 *via* their specific B-cell receptor and could engage both B-cell receptor and CD19/CD21/

CD81 (tetraspanin) signaling complexes simultaneously<sup>[41,42]</sup>. Furthermore, the HCV core protein induces IL-10 expression in mouse splenocytes<sup>[43]</sup> and IL-10 upregulates expression of IL-2R (Tac/CD25) in normal and leukemic B lymphocytes<sup>[44]</sup>. Therefore, IL-10 and IL-2R might induce B cell transformation and B-cell NHL. The induction of IL-2, IL-10, and Bcl-2 by the HCV core protein and the induction of IL-12 by E2 have been proposed as mechanisms that play a major role in lymphomagenesis<sup>[43]</sup>.

Striking geographic differences in the prevalence of lymphoproliferative disease have been found, suggesting that genetic and/or environmental factors are also involved in the pathogenesis of this disorder. The prevalence is higher in Italy, the United States, Brazil, and Japan, but not in other countries where the prevalence of HCV infection in the general population is lower, such as in Canada. A total of 100 patients with B-cell lymphoma (10 high grade 46 intermediate grade 44 low grade) and 100 controls with non-hematological malignancies were studied in North America. None of the controls or lymphoma patients had antibodies to HCV, suggesting that HCV is unlikely to play an important role in the pathogenesis of B-cell lymphoma in North America. In contrast, a study of another general population was performed in patients of second-generation Danish-Swedish origin, and it was found that the presence of HCV infection was a risk factor for the development of NHL despite the low prevalence of HCV infection in this population<sup>[10,18,45-51]</sup>. Factors that can contribute to geographic differences include the prevalence of HCV infection in the general population-HCV appears to be associated with B-cell NHL mainly in countries such as Italy, where HCV is highly prevalent<sup>[52]</sup>; HCV genotype<sup>[53]</sup>; and the type of virology testing used, since the detection of HCV antibodies without testing for HCV RNA may underestimate the true rate of HCV infection in NHL patients<sup>[54]</sup>.

### **Findings against the association between HCV and NLH**

In addition to the findings described above, data have been collected in recent years that argue against an association between HCV infection and lymphoproliferative disorders. One study from India showed that the incidence of HCV infection was 1% in patients with NHL and 0% in patients with chronic lymphocytic leukemia<sup>[55]</sup>. In another case-controlled study from Pakistan, the prevalence of HCV infection was not significantly different in 143 lymphoma patients compared with 29 controls (5% *vs* 3.4%, respectively)<sup>[56]</sup>. A prospective case-controlled study assessed whether HCV infection preceded the development of NHL by examining the serum of 95 subjects with NHL diagnosed at a mean 21 years after screening for anti-HCV antibodies and HCV RNA. In this study, samples from four of 95 case subjects and one of 95 matched control subjects had repeatedly reactive HCV enzyme-linked immunosorbent assay enzyme-linked immunosorbent assays. None of these cases, however, were confirmed HCV seropositive by third generation strip



immunoblot assay (RIBA-3). Furthermore, none of the serum samples from case subjects were found to be HCV RNA-positive by real time PCR (RT-PCR). Based on this study, HCV infection acquired during early adulthood was determined to not be a risk factor for subsequent B-cell neoplasia over the course of a patient's lifetime<sup>[49]</sup>.

Another study exploring the association between HCV and HBV infections with lymphoproliferative diseases<sup>[18]</sup> showed no significant association between the presence of anti-HCV antibodies and the risk of developing NHL, multiple myeloma, or Hodgkin's lymphoma. This study did find that chronic HBV infection may increase the risk of lymphoid malignancies.

In a prospective study of 2162 patients with HCV infection in Japan, the incidence of NHL was not considerably elevated (only four of the 2162 patients with HCV had NHL); however, the median follow-up time was less than 6 years. This short follow-up period may explain the low rate of NHL in this study since NHL may typically develop only after long-standing HCV infection<sup>[57]</sup>. In another study of 2,533 female patients infected with HCV, an association between HCV infection and NHL was not observed<sup>[58]</sup>.

Several studies have failed to find an association between HCV infection and lymphoma subtypes such as mucosa-associated lymphoid tissue lymphoma of the stomach<sup>[48,59-62]</sup>. Furthermore, a study of HIV-positive patients with concurrent HCV infection revealed that HCV infection was not associated with an increased risk of developing NHL. In addition, no relationship between NHL risk and anti-HBcAg or anti-HBsAg was found<sup>[19]</sup>.

## CONCLUSION

In conclusion, lymphomagenesis is a multifactorial process in which genetic, environmental, and infectious factors can all be involved.

The above review described some studies that found a strong association between HCV infection and the development of lymphoma, particularly non-Hodgkin lymphoma one of the regions for this strong association between HCV and lymphoproliferative disease can be due to the overrepresentation of lymphoplasmacytoid lymphomas/immunocytomas relative to other B-NHL histotypes in several studies is likely the result of a selection bias towards the inclusion of patients with type II MC in these centers, and this reason might account for the apparently high prevalence of HCV infection in B-NHL patients in these series<sup>[63]</sup>. The studies presented here that showed a lack of association between HCV infection and lymphoma may have been influenced by small sample size, short follow-up periods, and geographic variation. We believe this field of study would benefit from further prospective trials.

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