

Hepatitis C and Its Relation to B-Cell Lymphoma

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ABSTRACT: Hepatitis C virus (HCV) infection is a global health concern, with millions of people chronically infected. The course of this chronic disease may lead to lymphoproliferative disorders ranging from benign mixed cryoglobulinemia to malignant non-Hodgkin lymphoma (NHL). In this article, we reviewed the current knowledge of the different pathologic mechanisms involved in the occurrence of HCV-related lymphoproliferative diseases. Hepatitis C virus directly or indirectly causes different steps of progressive alterations. A chronic antigenic stimulation will select a B-cell clone that will gain immortality via alterations in coding DNA in proto-oncogenes and tumour-suppressor regions. The main challenge in the treatment of HCV-induced NHL is to obtain a sustained virologic response before HCV induced irreversible damages leading to everlasting cell survival. The new interferon-free therapies introduce a new era of management of HCV-NHL, with recent published data to be promising. Nevertheless, further studies are required to assess the safety of those drugs, particularly in association with chemotherapy.

KEYWORDS: hepatitis C virus, non-Hodgkin lymphoma, mixed cryoglobulinemia, lymphoproliferative diseases, treatment

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Introduction

Hepatitis C virus (HCV) is a positive single-stranded enveloped RNA virus which belongs to the Flaviviridae family, discovered in 1989. It replicates within the hepatocytes, causing its main clinical features, liver dysfunction, and increases the risk of hepatocellular carcinoma development. It also has the ability to infect other cells and tissues, such as lymphocytes. These peculiar characteristics explain the numerous extrahepatic clinical manifestations, including haematologic features such as mixed cryoglobulinemia (MC) and non-Hodgkin lymphoma (NHL). The course of virus in lymphocytes cells, as its presence is particularly noticed in peripheral blood mononuclear cells (PBMCs) and bone marrow, leads to chronic antigenic stimulation, cytokine productions, and altered molecular pattern that select a B-cell clone. Other indirect alterations of double-stranded DNA and its repair system complete the malignant transformation process. The multiple steps of the pathologic course of the HCV-infected B cells explain the usual indolent evolution of the disease, with a long-lasting presence of MC in the serum, either symptomatic or not, before the frank malignant NHL declares. Understanding these different steps, the therapeutic objective is to target the lymphoproliferation obtaining a sustained virologic response (SVR) by clearing the presence of the virus before the B-cell immortalization or adding conventional NHL treatments. The recent progress in antiviral therapy is a hope for a best prevention of lymphoproliferative complication of HCV chronic infection.

HCV Epidemiology

Hepatitis C virus infection is a global health problem affecting 3% of the world population, with a prevalence of around 150 to 170 million people estimated to be chronically infected worldwide.¹ However, the spread of the chronic infection varies among countries as the highest prevalence of infected people (>10%) is reported in Egypt, Central Africa, Mongolia, and Bolivia,² whereas Europe accounts for around 15 million people.³ The Asian continent accounts for the largest number of infected persons, China and India together having more HCV infections than the whole of Europe or America.⁴

HCV-Related Extrahepatic Manifestations

Chronically infected patients are at risk of developing liver complications, such as cirrhosis, liver failure, and liver cancer, with an estimated liver-related mortality of 350 000 people per year. However, the risks of morbidity and mortality have been underestimated until a recent period because they did not take into account the numerous – and sometimes severe – extrahepatic consequences of HCV infection. In some large cohort studies, up to 75% patients experienced HCV-related extrahepatic morbidity of different severity, from benign conditions as fatigue to disabling conditions as lymphoma.⁵ Some of these conditions are well documented and more common, ie, cardiovascular disease, kidney involvement, insulin resistance, diabetes mellitus, and neurocognitive dysfunction, whereas others (polyarthritis, pruritus, polymyositis, erythema nodosum, polyarteritis nodosa) are infrequent, or their association with HCV



has not yet been proven. The most common extrahepatic manifestation described in HCV-positive individuals is type II MC, whereas HCV infection is present in around 80% of patients with MC.⁶

HCV-Induced Mixed Cryoglobulinemia

Mixed cryoglobulinemia are immunochemically characterized as type II or type III cryoglobulins, which consist of polyclonal IgG with monoclonal or polyclonal IgM with rheumatoid factor (RF) activity, respectively, which precipitate in vitro at a temperature below 37°C.⁷ Hepatitis C virus infection is present in 80% to 90% of patients with MC,⁸ even in the absence of chronic liver disease. Hepatitis C virus core proteins and HCV RNA have been found within immune complexes.⁹

Epidemiologic studies on HCV-MC relationship show large differences in the geographic distribution, with higher prevalence in Southern Europe compared with Northern Europe or the United States. The MC clinical expression varies among patients, principally affecting the skin, with palpable purpura being the main symptom. Other frequent clinical features include the Raynaud phenomenon and acrocyanosis, neurologic manifestations (ranging from pure sensitive axonopathy to mononeuritis multiplex), and membranoproliferative glomerulonephritis. The severity of the affection ranges from benign symptoms such as arthralgia to potential dysfunction of vital organs such as glomerulonephritis or diffuse vasculitis.⁶

In large HCV-infected populations, about 50% of patients produce an MC, whereas 15% to 20% experience a symptomatic MC (MC vasculitis).^{10,11} Interaction between HCV and lymphocytes directly modulates B-cell and T-cell function and results in polyclonal activation and expansion of B-cell-producing IgM with RF activity.¹² CD4⁺ CD25⁺ FoxP3⁺ regulatory T cells, which have been shown to control autoimmunity, are significantly reduced in patients with HCV-MC vasculitis.¹³ This defect in immune regulation via T/B-cell interactions may play a role in the expansion of peripheral autoreactive B cells that lead to MC vasculitis.

The association between HCV infection and MC leads to the hypothesis that HCV may be involved in the pathogenesis of lymphoproliferative diseases. There are multiple factors predisposing HCV-infected patients to develop cryoglobulinemic vasculitis, and this condition is considered as an intermediate state before lymphoma development. The presence of MC in HCV-positive patients may increase the risk of developing NHL. A multicentre study showed an increased risk of over 35-fold for developing NHL in HCV-positive patients with symptomatic MC compared with the general population.¹⁴ Approximately 8% to 10% of patients with HCV-MC progress to NHL. Even after HCV eradication, HCV-MC patients remain at high risk to develop a B-NHL.¹⁵

HCV-Induced Non-Hodgkin Lymphoma

Pozzato et al¹⁶ and Ferri et al¹⁷ first described the association between HCV and NHL. The initial interest to investigate this

finding was driven by the known high prevalence of HCV in patients with MC. During the last 2 decades, the association between HCV and several haematologic malignancies, most notably NHL, was confirmed¹⁸ with a geographic gradient from north to south. At present, more than 10 000 cases of NHL have been screened for the presence of HCV infection, and several meta-analyses on the relationship between HCV and lymphoma have been published.¹⁹ Meta-analysis confirmed an increased risk of lymphoma in HCV subjects, with varying degrees of risk.²⁰ A recent review with 19 case-control studies included enrolled altogether 9038 cases and 12 224 controls. The pooled relative risk (RR) was 2.4 (95% confidence interval [CI]: 2.0-3.0), and most of them (11/19) showed a significantly elevated RR. The RR of the cohort studies was 2.0 (95% CI: 1.4-3.0). The overall RR estimation was 2.3 (95% CI: 1.8-2.9).²¹ These results confirm the increased risk of developing lymphoma in HCV-infected patients.

The most frequent subtypes of lymphomas associated with HCV infection are marginal zone NHL (MZL), especially splenic marginal zone lymphomas (SMZL), lymphoplasmacytic lymphoma, and diffuse large B-cell NHL (DLBCL), with odds ratio of 2.47, 2.57, and 2.24, respectively.¹⁹ A serum monoclonal gammopathy, more frequently IgM κ , diagnosed as monoclonal gammopathy of undetermined significance, was frequently observed in patients infected with HCV.²² A lower cumulative incidence of lymphoma development in patients who eradicated the virus confirms this association and suggests that HCV treatment could be a preventive measure.²³

The clinical course of the HCV-induced NHL is generally indolent. The most common feature of true HCV-induced NHL is the long-standing presence of MC and the late appearance of overt NHL, often after years of onset of the clinical symptoms of MC.

Sustained virologic response with interferon (IFN)-based treatment has been shown to induce NHL regression, whereas a viral relapse was followed by lymphoma recurrence.²⁴ These data are consistent with the regression of expanded B-cell clones following successful antiviral treatment and with the new expansion of the same clones in relapsers.²⁵ This regression was also shown in patients with benign lymphoproliferative conditions as MC, whereas a persistent B-cell clone, despite a clinical remission, was evidenced in SVR patients with splenic lymphoma with villous lymphocytes (SLVL).²⁶ This suggests the presence of no-return points in the HCV-driven lymphomagenesis, making the process progressively less dependent on the etiologic agent.²⁷

Physiopathology

Chronic B-cell stimulation

The presence of HCV proteins is a potent trigger for lymphoproliferation and clonal expansion of B cells (Figure 1). This is supported by the fact that most of the HCV-associated lymphomas are of germinal centre or postgerminal centre

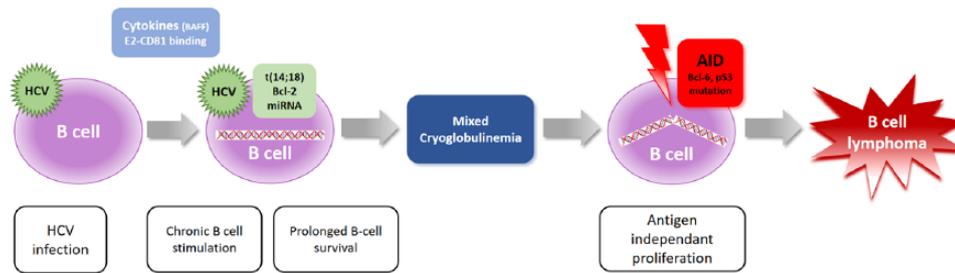


Figure 1. Physiopathology of lymphomagenesis in hepatitis C virus (HCV)-infected patients.

Hepatitis C virus infection leads to chronic stimulation and sustained activation of B cell through action of virus proteins (E2) binding to B-cell surface receptors (CD81) and an increased production of proinflammatory cytokines, especially autocrine BAFF. Virus protein core can modulate gene expression, upregulating miRNA or inducing translocations, such as t(14;18), involving antiapoptotic *Bcl-2* gene. These modifications lead to prolonged survival and clonal proliferation of B cells, associated with MC production.

Further steps in lymphomagenesis probably through other DNA damages involving proto-oncogenes and tumour suppressors lead to the development of a malignant B-cell clone.

origin.²⁸ The virus lymphotropism is sustained by the presence of HCV infection in the PBMCs and in the bone marrow.^{29,30}

Analysis of the V(D)J region of B cells derived from patients with MC and NHL supports the hypothesis that HCV proteins cause lymphoma through chronic antigenic stimulation. As mentioned above, the HCV-induced NHL often show a monoclonal IgM κ component²² and the presence of several autoantibodies, such as antinuclear, anticardiolipin, antithyroid, and anti-smooth muscle antibodies.^{5,6} At a molecular level, these patients use a restricted *IgHV* gene repertoire,³¹ with a strong bias for IgHV1-69 and V3-A27³² which encode the monoclonal IgM κ component.

Viral protein core is also involved in the chronic B-cell stimulation, and antibodies generated against the viral envelope protein E2 cross-react with the anti-IgG IgM RF which is isolated from patients with MC.³³ Ig-E2 complexes further stimulate RF-producing B cells. An important role of E2 is the binding to CD81 which serves as a receptor for HCV binding on the surface of B lymphocytes. Furthermore, E2 facilitates the assembly of the CD81/CD19/CD21 complex that lowers the cellular activation threshold.³⁴

Hepatitis C virus replication induces the release of cytokines, leading to lymphoproliferative signals. B-cell-activating factor (BAFF) of the tumour necrosis factor family (BAFF or B lymphocyte stimulator [BLyS]) plays an important role in B-cell maturation and can support the survival of autoreactive B-cell clones through the activation of nuclear factor kappa B (NF- κ B), Janus Kinase, and ERK pathways consecutively, leading to B-cell survival and proliferation. Hepatitis C virus infection itself can cause elevated BAFF levels.^{35,36} Sène et al showed that elevated BAFF levels in HCV-infected patients are associated with MC and NHL compared with HCV-negative individuals.^{37,38}

Other cytokines and cytokine receptors are responsible for B-cell proliferation in HCV infection, such as interleukin (IL)-17, IL-2, IL-10, and soluble IL-2 receptor.³⁹

These data support the hypothesis of an indirect, antigen-driven lymphoma development caused by HCV proteins in

agreement with pathogenesis of mucosa-associated lymphoid tissue (MALT) lymphoma caused by *Helicobacter pylori*. Mixed cryoglobulinemia may be an intermediate step to malignancy as the risk of developing HCV-induced NHL is higher in HCV-infected patients with MC.¹⁴ In addition, oligoclonal cell populations were found in patients with MC who consecutively developed NHL, as an evidence for a clonal chronic stimulation. Towards overt lymphoma, there might be an additional event, possibly a genomic alteration. A special translocation, t(14;18), involving the antiapoptotic *Bcl-2* gene is frequently detectable in patients affected by HCV-associated NHL, especially when associated with MC.^{40,41} Sometimes the translocation can be detected in a clonal B-cell population without the evidence of overt lymphoma. As a confirmation of the HCV infection involvement in that process, the presence of this population can be reversed with IFN-based antiviral treatment.⁴²

Direct intracellular damages

Hepatitis C virus core proteins can induce nitrogen oxide and reactive oxygen species production, which cause DNA breaks that can lead to genetic instability and be an additive mechanism in the transformation of B cells.⁴³ MicroRNAs (miRNAs) are short noncoding RNAs that bind to complementary sites of target messenger RNAs (mRNAs) and can modulate gene expression by either translational repression or mRNA degradation. A reduced expression of miR-26b has been found in HCV-positive versus HCV-negative patients with SMZL.⁴⁴ The diminution of the expression of miR-26b demonstrated an oncogenic potential in vitro and has been linked to a malignant tumour phenotype in hepatocellular carcinoma and lung carcinoma, breast cancer, and so on. One predicted target of miRNA26b is the NIMA-related kinase, NEK6, which has a critical role in mitotic cell cycle progression and is upregulated in various human cancers, such as hepatocellular carcinoma and lung, breast, colorectal, and laryngeal cancers.⁴⁵

Hit-and-run theory

A controversial point regarding the HCV-induced lymphoproliferative disorder pathway is the absence of evidence of virus replication inside the malignant clones in most of HCV-induced NHL. The chronic B-cell stimulation cannot explain alone all the malignant transformation process. Machida et al⁴⁶ found that HCV is able to induce a high mutation frequency of cellular genes (immunoglobulin heavy chain, *Bcl-6*, p53, and beta-catenin) in vitro by inducing double-strand breaks and by activating error-prone polymerases and activation-induced deaminase. These mutations balance the function of these cellular proto-oncogenes and tumour suppressors. The 'hit-and-run' theory consists of the occurrence of defect in DNA repair system leading to malignant transformation after these oncogenetic transformations, whereas the virus has already left the cell.

Multiple steps theory

It is more believed that it is all previously mentioned mechanisms combined that led to the development of HCV-associated NHL. As a first step, the antigenic stimulation caused by the replicating HCV leads to the selection of a B-cell clone and the development of MC. The second step in the establishment of a malignant clone is that the molecular damages induced by the virus protein core can be reversed by the viral clearance. Finally, in few patients, as a result of subsequent accumulation of additional mutations and genetic alterations, viral antigen is not necessary anymore and viral elimination is insufficient to avoid the development of malignant NHL.

Treatments

Indolent HCV-induced NHL

Antiviral therapy in HCV-related chronic hepatitis should aim at preventing hepatic and extrahepatic complications. Use of antiviral therapy for indolent asymptomatic HCV-induced NHL is widely accepted, supported by the European Society for Medical Oncology and the European Association for the Study of the Liver.^{47,48}

The treatment of chronic HCV infection has long been based on subcutaneous PEGylated IFN- α and oral ribavirin for a duration of 6 months for patients infected with HCV genotype 2 or 3 and 12 months for HCV genotype 1 or 4. The aim of treatment is to achieve an SVR (ie, HCV cure) defined as HCV RNA negativity (<12 UI/mL) 12 weeks after the end of antiviral therapy.

The use of antiviral therapy to treat HCV-associated lymphomas is based on the study by Hermine et al,⁴⁹ which was the first to show SLVL regression following HCV eradication with IFN-based antiviral therapy, whereas HCV-negative SLVL controls did not benefit from the same antiviral therapy. The impact of antiviral therapy on the course of HCV-induced

NHL is highlighted by a recent cohort study in Italy. From 704 consecutive HCV-positive patients with indolent NHL, 134 were managed with antiviral therapy for lymphoma control. Overall haematologic response rate was 77%, with 44% of complete response. For the entire cohort, the 5-year progression-free survival (PFS) was 48% (95% CI: 44%-53%), whereas it was 63% (95% CI: 50%-73%) for patients treated with antiviral therapy.⁵⁰ The use of rituximab (RTX) in HCV-induced NHL, alone or in combination with antivirals or chemotherapy (CT), might be interesting in low-grade NHL. It is highly active and well tolerated to treat indolent NHL⁵¹ and permits to achieve higher rate of MC clearance (68.4% vs 43.6%) and shorter time to clinical remission and better renal response rates when added to IFN-based therapy in patients with HCV-related MC.⁵²

HCV-induced DLBCL

Viral eradication cannot be the only option for aggressive DLBCL treatment. The addition of RTX to CT has been the major advance in the treatment of aggressive lymphomas in the last 2 decades. However, it is still not clear whether the addition of RTX to conventional CT is beneficial for the treatment of HCV-induced DLBCL, particularly because of the potential increase in hepatic toxicity. The largest prospective study, from Egypt, on 280 HCV-positive patients with DLBCL included 200 patients who received RTX plus CT and 80 patients who received CT only and found no significant difference in PFS and overall survival (OS). A severe hepatic toxicity was noted in 26.5% of RTX-treated patients versus 13.8% of those who received a CT alone ($P = .033$).⁵³

An Italian study on 535 patients treated with CT, associated with RTX in 255 cases, showed a 3-year OS of 71% in HCV-positive patients treated with cyclophosphamide, vincristine, prednisone, and doxorubicin plus RTX (R-CHOP). Severe hepatotoxicity occurred in 14% of patients but was not associated with the use of RTX.⁵⁴ A recent prospective study including 45 patients with HCV infection and DLBCL, all treated with R-CHOP, found a 3-year OS of 73%,⁵⁵ which is similar to the results found in HCV-negative DLBCL treated with R-CHOP. Antiviral therapy following CT-induced NHL remission permits to achieve a prolonged disease-free survival ($P = .038$).^{56,57}

New IFN-free antiviral therapies

With the development of new drugs able to induce earlier and better virologic responses, HCV treatment is now rapidly evolving, particularly in the case of HCV genotypes less responsive to traditional therapy with PEGylated IFN- α and ribavirin.⁵⁸⁻⁶⁰ A large amount of these patients can now quickly and efficiently be cured with new IFN-free therapy by sofosbuvir combined with simeprevir, daclatasvir, or ledipasvir or the combination of paritaprevir with ritonavir and ombitasvir with

or without dasabuvir.⁶⁰ The addition of ribavirin may shorten the duration of treatment. These agents have a better tolerability and a higher efficacy than IFN-based regimens.

A case report⁶¹ recorded the efficacy of 16-week IFN-free treatment combining the NS3/NS4 inhibitor faldaprevir with the nonnucleoside NS5B inhibitor deleobuvir and with ribavirin in a genotype 1 HCV-infected patient with SLVL. After a rapid virologic response (HCV RNA undetectable at week 4) without relevant side effects, a reduction in the lymphocyte counts was observed, and the spleen size returned to normal. The 1-year follow-up showed a maintained SVR and a persistence of clonal circulating lymphocytes, but no splenomegaly and other clinical manifestations of lymphoma.⁶¹

A very recent retrospective work by Arcaini et al⁶² reported data based on 42 HCV-infected patients with NHL (including 37 MZL) and 4 with chronic lymphocytic leukaemia who received IFN-free treatment (mostly sofosbuvir based), for a median duration of 12 weeks. The overall haematologic response rate was 67%, with 26% of complete response. The response rate among MZL was 73%. The estimated 1-year PFS was 75% (95% CI: 51%–88%). Seven out of 15 patients cleared MC.

These results highlight the importance of controlling HCV replication to remove the antigenic stimulation that can lead to lymphoma regression. Although IFN could have direct antilymphoma effects, good results with IFN-free regimens support the probable predominant antiviral action of IFN-based therapies. Although these results are promising, further research is required for HCV genotypes resistant to conventional treatment.

Conclusions

The spectrum of HCV-induced lymphoproliferative disorders goes from monoclonal gammopathy to MC and NHL. The frequent indolent course of the disease gives time to the physician for the choice of the most adapted therapy, according to the type of NHL. The cornerstone of treatment is to obtain an SVR. The new IFN-free therapies open a new era of management of HCV-infected patients and their complications. Nevertheless, further studies are needed to assess the safety of those drugs in association with CT.

AUTHOR CONTRIBUTIONS

All authors have contributed to the writing and reviewing of the contents of the manuscript.

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