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MINI REVIEW

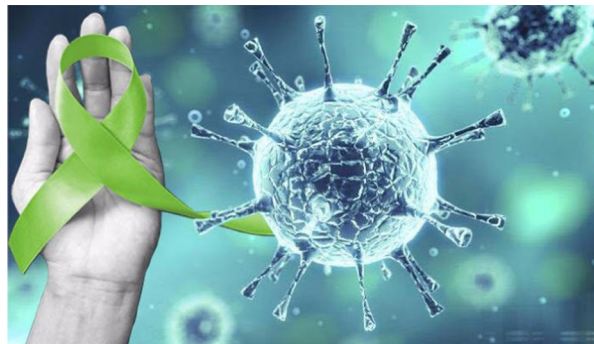# Hepatitis C virus and non-Hodgkin's lymphomas: A minireview

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G R A P H I C A L   A B S T R A C T

Malignant lymphomas and HCV infection have a dual relationship.

A R T I C L E   I N F O

A B S T R A C T

B-cell NHL is strongly associated with HCV that was proved in the last 2 decades. The most common HCV infection related B-NHL subtypes include MZL and DLBCL lymphomas. HCV-positive NHL patients usually present with older age at diagnosis, higher LDH, and more extranodal disease. The standard chemo-immunotherapy tolerance is generally good. Antiviral treatment achieves virological and hematological remission in HCV associated indolent lymphoma. More aggressive lymphoma requires combination of antiviral treatment and chemotherapy. New generation of HCV antiviral drugs is safe and is highly efficacious. Regi-

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mens including DAAs appear promising options as they can reduce the HCV-associated NHL incidence by dramatically lowering the HCV chronic carriers.

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Epidemiology

HCV is a hepatotropic, lymphotropic virus affecting over 180 million people, all over the world by chronic infection [1,2]. HCV infection usually results in chronic hepatitis leading to liver cirrhosis and hepatocellular carcinoma (HCC) in many patients [3]. In Egypt, the prevalence rate of HCV infected individuals was 872,000 (15% of the population) in 2013, with an estimated incidence of newly infected 125,000 viremic individuals each year [4], the rate which is considered as one of the highest prevalence rates of HCV worldwide [5,6]. HCV posi-

tive NHL patients' prevalence ranged from 0.5% to 25% as published by many series [7], while HCV infected NHL ranged from 26 to 42.1% in several Egyptian studies [8–11].

Route of HCV transmission

It is reported that the most common route of transmission among young population is drug use while the iatrogenic transmission was the predominant route in elder population in Northern countries and Southern countries, respectively [12]. In Egypt, high levels of HCV transmission was reported after parenteral anti-schistosomiasis treatment 3 decades before [13], but nowadays nosocomial route of transmission is the most predominant [14].

The relation between HCV and B-NHL

Large epidemiological studies had strengthened HCV and B-NHL link. In a systematic review published by Gisbert et al. the prevalence of HCV infection in B-NHL was identified in 5542 patients in 48 studies with a mean HCV infection rate of 13%. In another 10 case-control series, HCV prevalence in B-NHL was 17% compared to 1.5% in healthy controls. Therefore, HCV prevalence in patients with B-NHL was observed to be higher than the general population, denoting the role for HCV in of B-NHL etiology [15]. Subsequently, a meta-analysis of 15 studies on the relation between HCV infection and NHL demonstrated a collective relative risk of lymphoma of 2.5 (CI: (95%), 2.1–3.1) among HCV-infected subjects in 2006 [16]. The International Lymphoma Epidemiology Consortium (InterLymph) study reported collective results of HCV associate B-NHL. The study included more than eleven thousand subjects (6269 controls and 4784 cases) from 7 case-control studies conducted in the United States, Europe, and Australia. Among NHL cases, 172 (3.6%) had positive HCV infection versus 169 (2.7%) in controls (OR = 1.8; CI, 1.4–2.3). Thus overall, several studies have shown that HCV infection plays an important role in the development of definite subtypes of B-NHL indicating that genetic and environmental factors together with local HCV prevalence may be responsible for the geographically related results [17,18].

Common features of HCV associated B-NHL are extended duration of infection (15 years) and more frequent extranodal disease presentation. The most commonly reported B-NHL subtypes in different studies were marginal zone lymphoma, particularly splenic zone lymphoma, lymphoplasmacytic lymphoma, and DLBCL [19]. On the other hand, another study reported that DLBCL (62%) is the most common HCV related B-NHLs, followed by follicular lymphoma (13%) and MZL (11%) [20]. In Egyptian population, the relationship between chronic HCV infection and B-cell NHL was proved by Goldman et al. who conducted a case–control study at the NCI,

Cairo University. NHL cases (486 patients) were compared to controls (n = 786). The most common subtypes were of DLBCL (54.9%), followed by chronic lymphocytic leukemia (11.9%), follicular lymphoma (6.3%), T cell lymphoma, and mantle cell lymphoma (6.6%). HCV infection was positive in 27% of controls vs. 26–48% of NHL subgroups, with a significant association with diffuse large B cell, follicular lymphomas, and marginal zone (P < 0.001) [21].

Abu-Taleb et al. conducted a study that included 57 B-cell NHL patients with no previous chemotherapy. Fourteen patients (24.5%) had an indolent and 43 patients (75.4%) had an aggressive NHL. HCV infection was detected in 24 patients. Most of the patients with HCV infection (75%) presented with advanced stage (III/IV) compared to 42.5% among HCV negative cases (p-value = 0.09), and no statistically significant difference regarding age, sex, clinical presentation, stage, IPI score, PS status, LDH level, pathological type, or chemotherapy type was observed between the two groups [11].

Mechanisms of HCV-related lymphomagenesis

HCV is a single stranded RNA virus. HCV nucleic acid sequence integration into the host genome seems improbable due to the absence of reverse transcriptase. So, it can exert its oncogenic role indirectly by modulating of the host immune system [22]. Three possible theories can explain the process of HCV transformation including the following: (1) the external lymphocyte receptors are continuously stimulated by the viral antigen resulting in its proliferation; (2) replication of HCV occurs inside the B cells and then mediate their oncogenic effects through intracellular HCV proteins; and (3) "hit and run" theory which means permanent damage of B-cell, caused by the intracellular virus (e.g., mutation of tumor suppressor genes) [23].

Zekri et al. studied the NHL cases associated with HCV infection gene expression profile using c-DNA microarray. They studied 15,500 genes, out of which more than 1000 genes were differentially expressed either unregulated or down regulated. Also, HCV might rescue B lymphocytes from apoptosis, possibly through suppression of CASP1 and CASP4 and the anti-apoptotic BCL2 gene over expression. The genes such as BAL and MLLT3, which are myeloid/lymphoid leukemia and B cell lymphoma related were associated with HCV, that could influence the over expression of transcription regulator genes as TATA box binding protein (TBP) and may also influence the over expression of some immunoglobulin genes as immunoglobulin super family containing leucine gene in B cells resulting in overproduction of immunoglobulins in B-lymphocyte disorders. Moreover HCV was associated with MHC class II molecule reduced expression in B lymphocytes, and thus may result in inhibition of processing and presentation of the antigen through down regulation of different MHC class II molecule genes [24].

The chronic antigenic stimulation of HCV infection to the immune system is very similar to *Helicobacter pylori* pathogenesis in gastric MALT lymphoma as after *H. pylori* infection, and there is production of T cell-dependent responses through the classic reaction of germinal center, and consequently generates reactive B and T cells. Then, *H. pylori*-specific T cells start to migrate to the marginal zone/tumor area providing

non-related help to autoreactive neoplastic B cells involved in stimulation of CD40 and other surface receptors by cytokines and soluble ligands [25,26]. The possible role of proteins of the HCV envelope was studied which focused mainly on the HCV E2 protein (Fig. 1). E2 had been shown to interact with the tetraspanin CD81, which is also present on the B-cell surface. This binding causes lowering of the threshold and the B-cell activation thus causes sustained polyclonal B-cell activation [27,28].

Mixed cryoglobulinemia is a low-grade B cell clonal lymphoproliferative disorder that initially confined to the bone marrow and then transforms to aggressive malignant lymphoma in about 10% to 20% of patients after several years of diagnosis. Mixed cryoglobulinemia had been found to be closely related to HCV infection. Additionally, chromosomal aberrations may play a role in HCV-related lymphoproliferative disorders. The translocation of (14;18) was the most investigated genetic aberration that was found to be significantly related to type II or monoclonal MC [29]. The presence of t (14;18) translocation in mixed cryoglobulinemia was correlated with the antiapoptotic bcl-2 gene over expression in B-cells, that results in an imbalance of the Bcl-2/Bax ratio and abnormal survival of B-cell survival [30,31]. In many interventional studies, low-grade HCV-related NHL regression can occur with sustained virological response (SVR) to anti-viral treatment (AVT). Also the recurrence of lymphoma happened with the virus recurrence [32,33]. The involvement of some cancer-related and newly identified miRNAs, namely miR-155, miR-146a, miR-21 and miR26b has been confirmed in the pathogenesis of different subtypes of lymphomas including some HCV-related ones (MZL and DLBCL) [34–36] (Fig. 1) [37].

Treatment of HCV-associated B-cell NHL

Treatment of HCV-associated B-cell NHL remains to be optimized. Testing of serum antibody should be used first to assess exposure to HCV infection. Those patients who are seropositive should then be tested for HCV RNA to determine their viral load. Patients having the different subtypes of indolent NHL and HCV seropositivity, where there is no urgent need to start anti lymphoma therapy may benefit from starting with antiviral treatment as demonstrated in various publications [38–42].

In a large multicenter retrospective study, antiviral therapy with interferon ± ribavirin as a first line antiviral induced clearance of HCV-RNA in 80% of the patients (80/100) and in 67% (22/34) of the patients in whom AVT was received as second line [40]. In addition, lymphoma regression was occurred in large proportion of patients who received initial treatment with interferon ± ribavirin.

The addition of monoclonal antibodies to the classic front-line treatment of aggressive NHL CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone) had improved the lymphoma outcome. Rituximab plus CHOP (RCHOP) regimen is now the front line treatment for CD20 + DLBCL, This incorporation has been proved to improve the clinical outcomes and prognosis of those patients [43,44].

Thus, prior to the rituximab era, an earlier analysis of pooled data from GELA clinical studies suggested that HCV positive DLBCL may have dismal prognostic outcome due
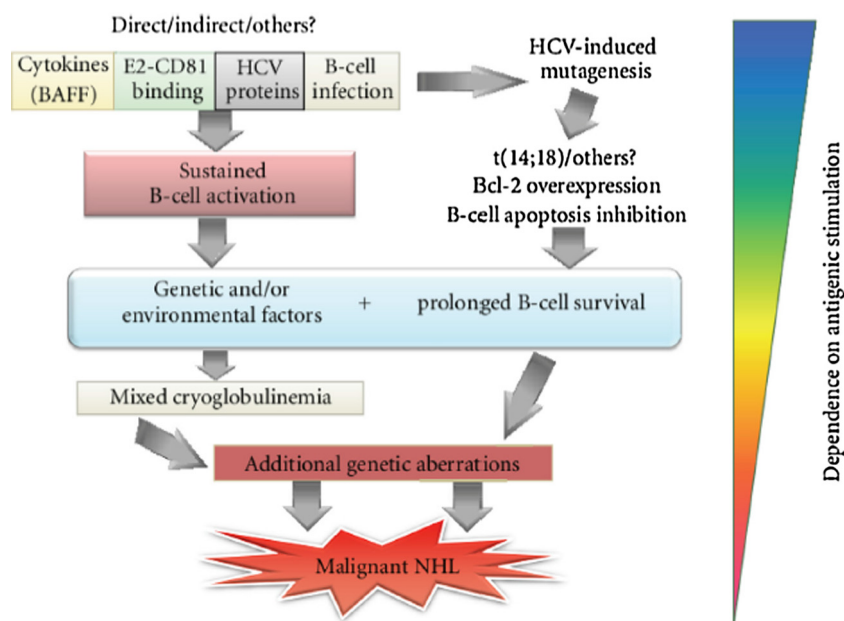
Fig. 1 Pathogenesis of HCV-related lymphomagenesis. Adopted from Zignego et al. [37].

to severe hepatic toxicity [45]. However, in the rituximab era consequent reports then showed that HCV positivity had no predictive role in terms of progression free or overall survival rates in DLBCL patients. However, more hepatotoxicity with chemoimmunotherapy was noticed among HCV-positive patients, which confirm the observation of previous GELA studies [46]. La Mura et al. conducted a retrospective study included 434 patients with indolent and aggressive NHL. Patients with HCV positive status treated with AVT (interferon-ribavirin) had better DFS than those who didn't receive the AVT (5-year DFS rates were 76% vs. 55%, respectively). In addition, patients with a SVR (sustained viral response) to AVT had no relapse ($n = 0/8$) compared with 29% for patients who did not respond to AVT ($n = 5$ of 17) [47].

The development of new antiviral agents had improved the treatment of chronic HCV infection. Combining the direct acting antiviral agents (DAA) with the standard AVT (pegylated interferon and ribavirin) had a significant improvement in the SVR rates in comparison with the standard AVT in chronic HCV carriers alone [48–51]. FDA recently approved the DAAs telaprevir and boceprevir for the treatment, in combination with pegylated interferon and ribavirin. Thus, the American Association for the Study of Liver Diseases (AASLD) updated the guidelines for the management of HCV infection and recommended to incorporate DAAs into standard AVT for patients infected with HCV [52].

In Egypt, we have conducted a retrospective study to elucidate the clinical characteristics of DLBCL patients in relation to HCV status. We included 132 DLBCL patients, with 64 (48.5%) and 68 (51.5%) of the patients who have received RCHOP and CHOP, respectively. Out of 132 DLBCL patients, HCV infection was positive in 35(26.5%). Patients with HCV infection had indistinguishable demography from HCV-negative patients except for more incidences of the presence of B symptoms and splenic involvement. Cox regression multivariate analysis showed that extra-nodal involvement, splenic involvement, and performance status were the independent predictors for inferior OS. But for adverse DFS, the presence of splenic involvement was the only independent prognostic factor.

The incidence of hepatitis flares was 40%, (14/35) among the HCV-infected patients vs. 9.3% (9/97) among the HCV-negative individuals ($P \leqslant 0.001$). Of the 35 HCV-positive patients, 14 (40%) received R-CHOP. HCV reactivation occurred in 34.2% (11/35 patients) without any relation to treatment regimen (7 (11%) for RCHOP and 5(7.3%) for CHOP; $p = 0.3$). No deaths had been reported due to hepatic toxicity. So, the clinical outcome of DLBCL patients was not affected by HCV infection and its reactivation has no relation to the type of treatment [10].

Prevention of HCV reactivation

Unlike HBV reactivation, no drugs are currently approved for the prevention of HCV reactivation in patients with HCV infection who undergo chemotherapy. However, the risk of HCV reactivation in such patients might be reduced by using lower doses of immunosuppressive drugs, close monitoring of ALT levels, and measuring HCV RNA levels early during episodes of potential viral reactivation. Given the possibility of immune-mediated hepatocyte injury upon HCV reactivation, some researchers have speculated that gradual tapering of immunosuppressants could be another strategy to prevent HCV reactivation [51–53]. Others tried using prophylaxis with the antiviral drug ribavirin with no clinical benefit [11]. Thus, it could not be recommended to use initial antiviral therapy in asymptomatic patients with HCV-positive low-grade B-cell NHL. For those with HCV genotype 1, triple antiviral therapy with inclusion of DAAs should be considered as per AASLD guidelines. Patients with HCV-positive aggressive B-cell NHL should initially be treated with appropriate chemo-immunotherapy regimens. Liver function and serum HCV RNA levels should be closely monitored during and after chemo-immunotherapy for development of hepatotoxicity.
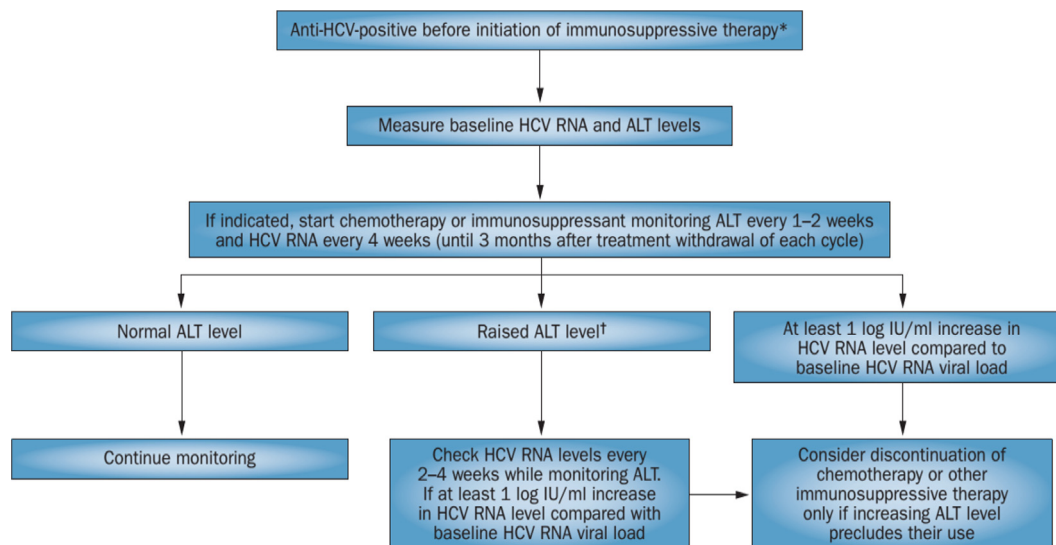
Fig. 2 An approach to the management of HCV positive cancer patients who are undergoing chemotherapy. Adopted from [55].

Antiviral therapy should then be considered in patients who achieve a CR after completion of chemo-immunotherapy. An approach to the management of HCV-positive patients with cancer who are undergoing chemotherapy or other immunosuppressive therapy is shown in Fig. 2. Chemotherapy can generally be administered in selected patients with HCV infection if they are monitored for viral reactivation during therapy [54].

Conclusions

HCV infection is a common disease worldwide, particularly in Egypt. One of its complications is the development of malignancy. On top of the list are hepatocellular carcinoma and malignant lymphomas. The optimal management of HCV-positive patients with NHL remains to be optimized. With the advent of new treatment molecules against HCV infection are showing better curative results, The hopes for lowering the incidence of the different malignant diseases caused as a complication of the viral infection, and improving their treatment outcomes is rising.

Conflict of Interest

The authors have declared no conflict of interest.

Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

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