Best Practice & Research Clinical Haematology xxx (2017) 1–9

Contents lists available at ScienceDirect

Best Practice & Research Clinical Haematology

journal homepage: www.elsevier.com/locate/beha

Hepatitis C virus – Associated marginal zone lymphoma

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Keywords:
Hepatitis C virus
Marginal zone lymphoma
Lymphomagenesis
Treatment

A B S T R A C T

The link between hepatitis C virus (HCV) infection and the development of B-cell non-Hodgkin lymphoma is now well established and based on a number of epidemiological studies. It is further supported by the observation of lymphoma regression after HCV eradication by antiviral treatment. The far most frequent entities are marginal zone lymphoma (MZL) and diffuse large B-cell lymphoma (DLBCL). MZL usually emerge on a background of mixed cryoglobulinemia, a low-grade lymphoproliferation, and often transform into DLBCL, thereby following a multistep oncogenesis process. The role of HCV in lymphomagenesis is not yet fully understood but several mechanisms have been proposed including (i) chronic external stimulation through the B-cell receptor and other surface receptors, and (ii) direct transformation by intracellular viral proteins, the former being probably predominant in MZL. Regression of HCV-associated MZL can be achieved with antiviral therapy and the novel generation of direct-acting antiviral agents appears highly effective and safe for the treatment of these lymphoma.

Introduction

The link between infectious agents and the development of marginal zone lymphoma (MZL) has been recognized for a long time. The prototypic example is that of *Helicobacter pylori* and gastric mucosa-associated lymphoid tissue (MALT)-type lymphoma, which involves a multistep pathogenesis process starting with clonal B cell expansion driven by chronic immune stimulation induced by the bacteria, followed by sequential acquisition of additional genetic abnormalities [1]. Importantly, in the early stages the lymphoma depend on the bacteria for their growth and tumor regression can be obtained with *H. pylori* eradication by antibiotics treatment, whereas this dependency is lost in later stages.

Hepatitis C virus (HVC) infection is a worldwide public health problem affecting an estimated 180 million individuals, but with important geographic variations [2]. In 15%–35% of patients, persistent chronic infection leads to hepatic fibrosis and cirrhosis and may ultimately evolve into hepatocarcinoma. A number of extrahepatic manifestations have also been reported, among which lymphoproliferative disorders are the most documented [3].

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http://dx.doi.org/10.1016/j.beha.2017.02.001
1521-6926/

HCV is a small encapsulated positive-stranded RNA virus of the *Flaviviridae* family. Its 9,6 kb genome is translated into a polyprotein of approximately 3000 aminoacids, which is further processed into 10 structural and non-structural proteins [4]. The former include the core capsid protein and two envelop proteins, E1 and E2. Most of the non-structural proteins (p7, NS2, NS3, NS4A, NS4B, NS5A and NS5B) are enzymes essential for HCV replication and constitute targets for new therapeutic agents. Six major serotypes, differing by their geographic distribution and responsiveness to antiviral treatment have been described.

Epidemiology of HCV-associated lymphomas

Early epidemiological studies reported conflicting results regarding the prevalence of HCV infection within patients with non-Hodgkin's lymphoma (NHL). High levels were found mainly in Italian cohorts (20%–40%) [5,6] and to a lesser extent in Japanese studies (8%–16%) [7,8]. In contrast, other European or Northern American studies failed to find any difference [9,10]. Discrepancies may have been explained, at least in part, by the relative small size of the cohorts, differences in methods used to detect the virus, HCV genotype distribution, as well as by environmental and/or genetic cofactors. Further epidemiological studies including large scale case–control cohorts and meta-analyses of retrospective series allowed to obtain a better assessment of the prevalence of HCV in NHL patients. They confirmed an increased although moderate risk of developing NHL in HCV-infected patients compared to HCV-negative controls (relative risk = 2–3) [11–13]. Thus, up to 10% of NHL can be associated with HCV in countries with high prevalence of the virus [11,14]. Pozzato et al. have recently conducted a meta-analysis on 19 case-controls and 4 cohort studies including in total about 9000 lymphoma cases (and over 12,000 controls) screened for the presence of HCV infection [15]. They found that HCV infection was associated with an overall 2.3 relative risk of developing NHL. There was however geographical heterogeneity linked to different prevalence of HCV infection within the population, with higher relative risk of NHL (>3) being observed in regions with high prevalence of infection such as the Mediterranean basin.

Besides regional differences, the prevalence of HCV infection may also vary according to the lymphoma histological subtype. A large meta-analysis from the International Lymphoma Epidemiology Consortium (InterLymph) identified 172 HCV-positive cases among 4784 NHL [16]. HCV was found to be associated with MZL (odds ratio [OR], 2.47; 95% confidence interval [CI], 1.44–4.23), diffuse large B-cell lymphoma (DLBCL) (OR, 2.24; 95% CI, 1.68–2.99), and lymphoplasmacytic lymphoma (OR, 2.57; 95% CI, 1.14–5.79). In contrast, there was no increased risk for follicular lymphoma (OR, 1.02; 95% CI, 0.65–1.60). Other studies also ruled out an association of HCV with chronic lymphocytic leukemia (CLL), Hodgkin's lymphoma or T-cell lymphoma [12]. Michot et al. recently reported the histological characteristics of 116 HCV positive B-cell NHL cases [17]. MZL and DLBCL were by far the two most frequent subtypes (39% each) confirming previous studies [12,15,16]. Interestingly in more than a third of cases, there was evidence that DLBCL originated from a low-grade NHL (mainly MZL) due to the presence of small neoplastic B cells infiltration in the tissue biopsies, confirming previous findings [18]. Altogether these data indicate that (i) MZL is probably the most frequent entity associated with HCV infection, and (ii) might be particularly prone to transform into aggressive DLBCL.

Characteristics of HCV-associated MZL

HCV-associated MZL develop following a long duration of infection with median time ranging from 15 to 25 years. A recent study including 45 MZL cases found that they frequently displayed bone marrow and/or blood (45%) and spleen (44%) involvement [17]. When compared to DLBCL, MZL presented more often with cryoglobulinemia (75% vs 44%) and rheumatoid factor (68% vs 35%).

All 3 subtypes of MZL, i.e. MALT, nodal and splenic have been found to occur in HCV infected patients [6,17,19,20]. Although HCV-positive gastric MALT have been reported [6], HCV infection seems to occur more frequently in non-gastric MALT. Arcaini et al. reported a series of 60 non-gastric MALT in which the most frequent localizations were the skin (35%), salivary glands (25%) and orbit (15%) [19]. In addition, HCV-associated MZL may present with distinctive characteristics. Saadoun et al. described 18 cases of splenic lymphoma with villous lymphocytes (SLVL) and type II cryglobulinemia and proposed it could represent a new entity [21]. Most of these patients were women (78%) and had symptomatic cryglobulinemia (72%). Paulli et al. reported 12 cases with an unusual subtype of MALT-type MZL, consisting in a sub-cutaneous “lipoma-like” presentation, also occurring predominantly in women (83%) and associated with an indolent clinical course [22].

Linking HCV infection to B-cell clonal proliferations

Mixed cryoglobulinemia: a pre-lymphoma stage

Mixed cryoglobulinemia (MC) is the most frequent extra-hepatic manifestation of HCV infection. Cryoglobulins are serum immunoglobulins (Ig) which precipitate at temperature below 37 °C. Depending on their composition they are classified as type I if only a single monoclonal Ig is present, or as MC which combine polyclonal IgG and either monoclonal (type II) or polyclonal (type III) IgM [23]. A very high prevalence of HCV infection (>90%) is found among patients with type II MC [24]. Conversely MC are detected in 30%–60% of patients of HCV-positive subjects, but with wide geographical heterogeneity [25,26]. In HCV-infected patients, they are usually present at low levels and symptomatic MC with clinical signs of vasculitis

Please cite this article in press as: Armand M, et al., Hepatitis C virus – Associated marginal zone lymphoma, Best Practice & Research Clinical Haematology (2017), http://dx.doi.org/10.1016/j.beha.2017.02.001