DOWNLOAD PDF ETIOLOGICAL ROLE OF HEPATITIS C VIRUS IN LYMPHOMAGENESIS

Chapter 1 : - NLM Catalog Result

*Etiological Role of Hepatitis C Virus in Lymphomagenesis [Gasztonyi Beata, Alajos Par, Kiss Katalin, Kereskai Laszlo, Gyula Mozsik] on blog.quintoapp.com *FREE* shipping on qualifying offers. Considering chronic hepatitis C virus (HCV) infection as a systemic disease, the authors (all of the U. Medical School.*

This article has been cited by other articles in PMC. Abstract Apart from its well known role as an etiological agent for non-A and non-B viral hepatitis, there is growing evidence that hepatitis C virus is associated to B-cell non-Hodgkin lymphoma. The association between HCV and lymphoproliferative disorders has been recently postulated based on epidemiological data, biological studies and clinical observations. The causative role of HCV in those disorders has been further supported by the response to antiviral therapy. Despite a better understanding of pathophysiological processes at stake leading from HCV infection to overt lymphoma, many issues still need to be further elucidated. Although HCV has been demonstrated to directly infect peripheral blood mononuclear cells both in vitro and, in some cases, in vivo, a strong body of evidence rather supports the hypothesis of an indirect transformation mechanism by which sustained antigenic stimulation leads from oligoclonal to monoclonal expansion and sometimes to lymphoma, probably through secondary oncogenic events. Here, we review epidemiological and biological studies, as well as clinical data on antiviral therapy, linking HCV-infection to B-cell non-Hodgkin lymphoma. The virus lacks a reverse-transcriptase and its genome encodes a single open reading frame for a large polyprotein, which is subsequently cleaved to structural and non-structural enzymatic component viral proteins. For more than a decade, evidence from either epidemiological studies, therapeutic approaches or biological data have emerged giving strong support to an etiological role of HCV in non-Hogkin lymphoma NHL development 1 , 2. Furthermore, HCV-associated NHL response to interferon IFN and ribavirin therapy in case of viral load decrease, previously described in several studies, also gave strong support for an etiopathological role of HCV in this kind of lymphoproliferative disorder. Although HCV is the major etiologic agent of non-A and non-B chronic hepatitis, it can present with a broad spectrum of extrahepatic manifestations. Among them, immune-related disorders have been described such as type II mixed-cryoglobulinemia MC , characterized by a monoclonal IgM with rheumatoid factor RF activity i. Among pathogenetic hypotheses, HCV lymphotropism has been studied but no direct transformation leading to an overt lymphoproliferative disorder has been clearly demonstrated. Conversely, strong evidence for an indirect role for HCV in inducing lymphoproliferative disorders has been given by recent findings. In this regard, association between HCV-infection, mixed cryoglobulinemia MC and NHL lent support to a multistep model in which HCV would induce a protracted stimulation of antigen-specific B-cell clones, leading to MC and in a subset of patients to overt lymphomas. Thus, cumulative evidence for a pathological link between HCV infection and lymphoma has emerged and will be reviewed in this paper. Early studies based on relatively small number of patients provided conflicting results and suggested a significant increased risk of B-NHL in HCV-infected patients only in high prevalence areas. This might be explained, at least in part, by a large difference in HCV prevalence itself which is lower in those countries , or by yet unknown environmental and genetic factors. It thus appears that there is a greater propensity to develop NHL in the setting of HCV infection, and that the risk is most dramatically evident in populations with high HCV prevalence. Besides, geographic variability worldwide may indicate additional important environmental factors influencing the strength of this relationship. Interestingly, during the same period following antiviral therapy, none of the patients who cleared the virus developed NHL whereas those who remained PCR positive had the same risk as not treated patients. However, despite these epidemiological and clinical evidences, the role of HCV in lymphomagenesis has remained elusive, and only recently have pathophysiological models started to emerge. Hence, in , we reported the outcome of 9 patients who had splenic MZL with villous lymphocytes and HCV infection treated with interferon alfa-2b IFN alone or in combination with ribavirin. Histologically, the lymphoid marginal zone surrounding the follicular areas is

expanded by neoplastic cells that have cytological and phenotypical features of marginal zone B cells. From a clinical point of view, the disease displays an indolent evolution with splenomegaly increasing over years and with a gradual progression of circulative malignant B cells. Of the 9 IFN-treated patients, 7 achieved a complete hematological remission, defined by the absence of abnormal lymphocytosis and the resolution of the splenomegaly, after HCV RNA load became undetectable. The remaining 2 patients experienced a partial or a complete response after addition of ribavirin and the loss of detectable HCV RNA. Conversely, none of 6 similarly treated HCV-negative SLVL patients responded to therapy thereby suggesting that the observed response rate was not due to the effect of interferon itself. Those results gave support to the hypothesis that HCV might trigger, to some extent, clonal expansion and oncogenic events at least in a subgroup of indolent lymphomas patients. All patients were treated with alpha-IFN with 10 patients or without 8 patients ribavirin. Four patients had received prior therapy for SLVL including splenectomy or chemotherapy. Six patients received associated therapy for symptomatic MC steroids, cyclophosphamide or plasmapheresis. Two patients with major virological responses more than 2 log reduction in HCV RNA also achieved complete hematological remission, whereas the 2 patients with minor virological responses less than 2 log reduction in HCV RNA only achieved partial hematological responses i. Moreover, in one patient with a virological relapse, villous lymphocytosis reappeared, but re-initiation of antiviral therapy was associated with a second complete hematological remission following HCV RNA reduction. The mean time to treatment responses was approximately 4 months for both virological and hematological responses. Mean duration of antiviral treatment was 17 months. Responses were sustained, as the mean duration of hematological response was 62 months. Clinical manifestations of MC subsided in all patients after antiviral treatment. Interestingly, viral genotype did not seem to correlate with the response as 4 out of 7 patients presenting with HCV genotype 1, usually associated with poor responses, achieved a complete hematologic response. Of note, even for patients who exhibited a complete hematological remission, B-cell clone could still be detected in peripheral blood but clinical relapses did not occur if viremia remained negative.

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Chapter 2 : Medical Online Books - TermÃ©k

1. Author(s): Gasztonyi,BeÃ¡ta, Title(s): The etiological role of hepatitis C virus in lymphomagenesis: (a clinical study)/ by BeÃ¡ta Gasztonyi.

Medit J Hemat Infect Dis , 2 1: The association between HCV and lymphoproliferative disorders has been recently postulated based on epidemiological data, biological studies and clinical observations. The causative role of HCV in those disorders has been further supported by the response to anti-viral therapy. Despite a better understanding of pathophysiological processes at stake leading from HCV infection to overt lymphoma, many issues still need to be further elucidated. Although HCV has been demonstrated to directly infect peripheral blood mononuclear cells both in vitro and, in some cases, in vivo, a strong body of evidence rather supports the hypothesis of an indirect transformation mechanism by which sustained antigenic stimulation leads from oligoclonal to monoclonal expansion and sometimes to lymphoma, probably through secondary oncogenic events. Here, we review epidemiological and biological studies, as well as clinical data on antiviral therapy, linking HCV-infection to B-cell non-Hodgkin lymphoma. The virus lacks a reverse-transcriptase and its genome encodes a single open reading frame for a large polyprotein, which is subsequently cleaved to structural and non-structural enzymatic component viral proteins. For more than a decade, evidence from either epidemiological studies, therapeutic approaches or biological data have emerged giving strong support to an etiological role of HCV in non-Hogkin lymphoma NHL development [1,2]. Furthermore, HCV-associated NHL response to interferon IFN and ribavirin therapy in case of viral load decrease, previously described in several studies, also gave strong support for an etiopathological role of HCV in this kind of lymphoproliferative disorder. Although HCV is the major etiologic agent of non-A and non-B chronic hepatitis, it can present with a broad spectrum of extrahepatic manifestations. Among them, immune-related disorders have been described such as type II mixed-cryoglobulinemia MC , characterized by a monoclonal IgM with rheumatoid factor RF activity i. Among pathogenetic hypotheses, HCV lymphotropism has been studied but no direct transformation leading to an overt lymphoproliferative disorder has been clearly demonstrated. Conversely, strong evidence for an indirect role for HCV in inducing lymphoproliferative disorders has been given by recent findings. In this regard, association between HCV-infection, mixed cryoglobulinemia MC and NHL lent support to a multistep model in which HCV would induce a protracted stimulation of antigen-specific B-cell clones, leading to MC and in a subset of patients to overt lymphomas. Thus, cumulative evidence for a pathological link between HCV infection and lymphoma has emerged and will be reviewed in this paper. Early studies based on relatively small number of patients provided conflicting results and suggested a significant increased risk of B-NHL in HCV-infected patients only in high prevalence areas. This might be explained, at least in part, by a large difference in HCV prevalence itself which is lower in those countries , or by yet unknown environmental and genetic factors. It thus appears that there is a greater propensity to develop NHL in the setting of HCV infection, and that the risk is most dramatically evident in populations with high HCV prevalence. Besides, geographic variability worldwide may indicate additional important environmental factors influencing the strength of this relationship. Interestingly, during the same period following antiviral therapy, none of the patients who cleared the virus developed NHL whereas those who remained PCR positive had the same risk as not treated patients. However, despite these epidemiological and clinical evidences, the role of HCV in lymphomagenesis has remained elusive, and only recently have pathophysiological models started to emerge. If HCV infection has been inferred to be a factor in the development of NHL on the basis of case-control epidemiological studies as previously discussed, strong line of evidence also arose from response of so called HCV-associated lymphoma to antiviral therapy. Hence, in , we reported the outcome of 9 patients who had splenic MZL with villous lymphocytes and HCV infection treated with interferon alfa-2b IFN alone or in combination with ribavirin. Histologically, the lymphoid marginal zone surrounding the follicular areas is expanded by neoplastic cells that have cytological and

phenotypical features of marginal zone B cells. From a clinical point of view, the disease displays an indolent evolution with splenomegaly increasing over years and with a gradual progression of circulative malignant B cells. Of the 9 IFN-treated patients, 7 achieved a complete hematological remission, defined by the absence of abnormal lymphocytosis and the resolution of the splenomegaly, after HCV RNA load became undetectable. The remaining 2 patients experienced a partial or a complete response after addition of ribavirin and the loss of detectable HCV RNA. Conversely, none of 6 similarly treated HCV-negative SLVL patients responded to therapy thereby suggesting that the observed response rate was not due to the effect of interferon itself. Those results gave support to the hypothesis that HCV might trigger, to some extent, clonal expansion and oncogenic events at least in a subgroup of indolent lymphomas patients. All patients were treated with alpha-IFN with 10 patients or without 8 patients ribavirin. Four patients had received prior therapy for SLVL including splenectomy or chemotherapy. Six patients received associated therapy for symptomatic MC steroids, cyclophosphamide or plasmapheresis. Two patients with major virological responses more than 2 log reduction in HCV RNA also achieved complete hematological remission, whereas the 2 patients with minor virological responses less than 2 log reduction in HCV RNA only achieved partial hematological responses i. Moreover, in one patient with a virological relapse, villous lymphocytosis reappeared, but re-initiation of antiviral therapy was associated with a second complete hematological remission following HCV RNA reduction. The mean time to treatment responses was approximately 4 months for both virological and hematological responses. Mean duration of antiviral treatment was 17 months. Responses were sustained, as the mean duration of hematological response was 62 months. Clinical manifestations of MC subsided in all patients after antiviral treatment. Interestingly, viral genotype did not seem to correlate with the response as 4 out of 7 patients presenting with HCV genotype 1, usually associated with poor responses, achieved a complete hematologic response. Of note, even for patients who exhibited a complete hematological remission, B-cell clone could still be detected in peripheral blood but clinical relapses did not occur if viremia remained negative. Although epidemiological studies and clinical data link NHL with HCV, underlying biological processes ultimately leading from infection to lymphoma are still poorly understood. Nevertheless, antigen-driven lymphoproliferation might be though of as being split into 2 distinct mechanisms. In most cases, these anomalies alarm the DNA damage response system that either allows for DNA repair or eliminates the aberrant B-cell clones. As regards to hepatitis C virus, few experimental data support the hypothesis of a direct transformation mechanism accounting for HCV-associated lymphomagenesis. In in vitro studies, CD81 has been shown to be an entry receptor for HCV and could be involved in infection of B cells by the virus. Similarly, frequent chromosomal polyploidy in peripheral blood mononuclear cells PBMC from HCV-positive patients was recently demonstrated, as well as in splenocytes from HCV core protein-expressing transgenic mice, suggesting that HCV infection may inhibit the mitotic checkpoint. Therefore, identification of negative strand RNA sequences in cells is indicative of active virus replication. So far, direct infection of the malignant clone has been described in a single case of B-cell lymphoma associated with HCV. On the contrary, many studies support the role of HCV as an indirect transformation agent by chronically stimulating B-cell immunologic response and ultimately leading to overt lymphoma in some cases. Along with data on the response of lymphoma to therapy, antiviral treatment has been associated with disappearance of MC and in many cases of B-cell clones. Nevertheless, NHL does not always evolve out of MC in what can be thought of as a stepwise evolution and many issues still need to be further elucidated. Other recent data support a major role for HCV envelope glycoprotein E2 in indirect transformation. To further support this hypothesis, direct infection of lymphocytes by HCV would not be necessary in vivo to induce somatic mutations of several oncogenes and tumor suppressor genes such as p53, beta-catenin and Bcl6 as recombinant HCV E2 binding to surface CD81 has also been shown to induce somatic hypermutation of the immunoglobulin gene locus Figure 3B. Altogether, those biological data have led to the concept of a multi-step lymphomagenesis process in HCV-related B-cell clonal disorders by an indirect transformation mechanism. The finding that MC represents an independent risk factor for the development of NHL in

HCV-infected patients, [42]]as well as the finding that, among HCV-infected patients with NHL, antiviral treatment was more effective in those with associated MC16 lend support to a model in which HCV would induce a protracted stimulation of antigen-specific B-cell clones, leading to MC and in a subset of patients to overt lymphomas. Besides chronic antigenic stimulation, cytokines and growth factors produced within the inflammatory context of chronic infection are now suspected to play a key role in B-cell transformation. The balance between IL17 expected role in protective immunity to HCV and its demonstrated role in inducing autoimmunity has to be further studied in MC and NHL HCV-positive patients to bring new insights into the pathogenesis of these disorders. Concerning oncogenic events leading to NHL development, cytogenetic information on HCV-associated lymphomas is scarce. Conversely, 2q loss was associated with more aggressive B-cell lymphomas 4 out of 5 DLBCL with no response to antiviral treatment. Response to treatment from our cohort of patients illustrated the hypothesis of additional oncogenic events driving oligoclonal proliferation in MC to monoclonal expansion in lymphoma. Accordingly, despite the efficacy of antiviral treatment in a majority of patients, leading to complete virological and hematological responses including the disappearance of detectable MC, the B-cell clones were still detectable in all patients. In the latter, B-cell clones are therefore likely to have accumulated unknown additional oncogenic events, inducing a survival benefit for this expanded clonal population that remains however still dependent upon antigenic stimulation as demonstrated by response to antiviral treatment. Surprisingly, patients in the HCV-positive group exhibited a longer event-free survival although the overall survival was significantly shorter in HCV positive patients. Conclusions Among the many extrahepatic manifestations of HCV, the interactions of the virus with B cells and their subsequent diseases are major consequences of chronic HCV infection. In some cases, the restricted B-cell response to HCV might undergo an oncogenic event giving survival advantage to a subclonal population, which may ultimately lead to a frank lymphoproliferative disorder. Evidence indicates a potential infection of the B-cell compartment in HCV-positive patients but it is likely an indirect transformation process that accounts for HCV-associated lymphoproliferative disorders. HCV associated MC, low-grade B-cell lymphomas and particularly SLVL and a subset of large B-cell lymphomas can fit in a continuum whereby chronic antigenic stimulation by persistent viral replication leads to progressive and antigen-driven B-cell transformation. These different stages could correspond to a step-by-step model of B-cell lymphomagenesis, ultimately leading to complete transformation and loss of antigen-dependence as seen in DLBCL. MC could thus be viewed as a marker of antigen-dependence of the lymphoproliferation. Several lines of evidence strongly suggest that antiviral therapy should be considered as first-line therapy in HCV-associated lymphomas, especially in the presence of MC. Because of its clinical implications, HCV related low grade lymphoma should be classified as a special entity as it has been proposed in the World Health Organization lymphoma classification for T-cell lymphoproliferation related to HTLV Acknowledgments Authors are indebted to Veronique Bachy for her assistance in reviewing the manuscript. Hepatitis C virus infection in subsets of neoplastic lymphoproliferations not associated with cryoglobulinemia. Hepatitis C virus infection in patients with B-cell non-Hodgkin lymphoma. No association between hepatitis C and B-cell lymphoma. The role of hepatitis C virus in the aetiology of non-Hodgkins lymphoma--a regional association? Risk of non-Hodgkin lymphoma and lymphoproliferative precursor diseases in US veterans with hepatitis C virus. Hepatitis C and risk of lymphoma: Dal Maso L, Franceschi S. Hepatitis C virus and risk of lymphoma and other lymphoid neoplasms: Cancer Epidemiol Biomarkers Prev. Hepatitis C and non-Hodgkin lymphoma among cases and controls from the International Lymphoma Epidemiology Consortium. Most cases of primary salivary mucosa-associated lymphoid tissue lymphoma are associated either with Sjoegren syndrome or hepatitis C virus infection. Splenic and nodal marginal zone lymphomas are indolent disorders at high hepatitis C virus seroprevalence with distinct presenting features but similar morphologic and phenotypic profiles. Regression of splenic lymphoma with villous lymphocytes after treatment of hepatitis C virus infection. N Engl J Med. Splenic lymphoma with villous lymphocytes: Splenic lymphoma with villous lymphocytes, associated with type II cryoglobulinemia and HCV infection: Response to antiviral treatment in

hepatitis C virus-associated marginal zone lymphomas. Haematological associations of Epstein-Barr virus infection. New therapeutic approaches for adult T-cell leukaemia. Boshoff C, Weiss R. Infection-associated lymphomas derived from marginal zone B cells: Chromosomal translocations deregulating c-myc are associated with normal immune responses. Role of genomic instability and p53 in AID-induced c-myc-Igh translocations. Binding of hepatitis C virus to CD Hepatitis C virus infection activates the immunologic type II isoform of nitric oxide synthase and thereby enhances DNA damage and mutations of cellular genes. Hepatitis C virus induces a mutator phenotype: Hepatitis C virus causes uncoupling of mitotic checkpoint and chromosomal polyploidy through the Rb pathway.

Chapter 3 : Pathogenetic Mechanisms of Hepatitis C Virus-Induced B-Cell Lymphomagenesis

The hepatitis C virus (HCV) was discovered in , which is dominantly transmitted via of blood transfusion or of intravenous medicine. The etiological role of HCV has gradually increased in Hungary and in the World, which produces acute (hepatitis) and chronic (hepatitis, liver cirrhosis, hepatocellualr carcinoma) liver diseases.

 Although the liver is considered to be the primary target, extrahepatic manifestations are well recognized among patients with chronic HCV infection. The clinical evidence that antiviral therapy has a significant role in the treatment at least of some HCV-associated lymphoproliferative disorders, especially indolent B-NHL, further supports the existence of an etiopathogenetic link. However, the mechanisms exploited by HCV to induce B-cell lymphoproliferation have so far not completely clarified. During its replicative cycle it goes through a negative-stranded RNA, but not DNA, intermediate, so that integration of HCV nucleic acid sequences into the host genome seems unlikely. The HCV envelope proteins consist of two heavily glycosylated proteins, E1 and E2, which act as the ligands for cellular receptors [1 , 2]. CD81 is a widely distributed cell-surface tetraspanin that participates in different molecular complexes on various cell types, including hepatocytes, B-lymphocytes, T-lymphocytes, and natural killer cells. It has been proposed that HCV exploits CD81 not only to invade hepatocytes but also to modulate the host immune responses [5]. HCV is a well-recognized etiologic agent of chronic hepatitis. Indeed, the risk of HCC in the HCV-infected population is 23â€”35 times higher than in noninfected healthy individuals [8 , 9]. The possible pathogenetic mechanisms of HCV-induced B-cell lymphomagenesis are reviewed. Epidemiologic Association of HCV and B-NHL Evans and Mueller proposed that either epidemiologic or virologic guidelines need to be fulfilled to support an etiologic role for a virus in a given human cancer [17]. Suggested epidemiologic guidelines included the following: Suggested virologic guidelines included the following: As far as the association between HCV infection and occurrence of B-NHL is concerned, most of the epidemiologic guidelines for causality from Evans and Mueller are met. The possibility is raised that in these latter geographic areas where HCV prevalence among subjects not affected with B-NHL is low, the spread of the virus may be recent, thus not allowing the full consequences on B-NHL development to be observed. Furthermore, HCV infection often precedes by years the occurrence of lymphomas [26]. Another meta-analysis reviewed data from 23 studies 4, NHL patients and 1,, controls and found a stronger association odds ratio 5. Conversely, one of the largest case-control studies to date found a higher OR 3. The possible association between specific viral genotypes and malignant lymphoproliferative disorders remains a controversial issue. There are at least six major HCV genotypes whose prevalence varies geographically. Genotype 1 accounts for the majority of infections in North America, South America, and Europe [7]. Various clinical studies failed to demonstrate a link between specific viral genotypes and B-NHL, but it should also be noted that this issue was not specifically addressed in several other series. Recent epidemiologic evidence from a multicenter retrospective study also suggested that genotype 2 may be more prevalent and carcinogenic in lymphoma patients [34]. In details, HCV-positive patients were classified as cancer patients patients, including 53 hematologic malignancies and 76 solid tumors , immunocompetent subjects and HCV-HIV coinfected patients. Interestingly, Pellicelli et al. Because HCV genotype 2 is associated with a longer duration of viral infection, it has been speculated that over time it may induce a persistent chronic immunostimulation of B-cells. On the contrary, direct lymphocyte transformation could be hypothesized for HCV genotype 1 in aggressive lymphomas, on the basis of the shorter duration of viral exposure [19]. Future perspective studies enrolling a large number of patients are warranted to further investigate the different distribution and carcinogenic potential of different HCV genotypes. The regression of HCV-related B-NHL following antiviral therapy probably represents the strongest argument in favor of an etiologic link between HCV infection and certain human lymphomas [16 ,

26]. Several clinical trials showed that antiviral therapy, mostly based on peg-interferon and ribavirin, resulted in either complete or partial remissions of lymphoma in HCV-positive but not HCV-negative B-NHL patients [29 , 35 â€" 37]. Lymphoma regression was usually positively correlated with viral load reduction [29]. These trials have been conducted in asymptomatic indolent lymphomas during a phase in which no other therapeutic intervention was administered. For aggressive lymphoma or symptomatic indolent lymphoma, HCV eradication alone is not an option. These patients require systemic therapy with rituximab and chemotherapy-based regimens as first treatment. Nevertheless, antiviral therapy to eradicate HCV may be an option after successful lymphoma therapy. Whether HCV eradication after-chemoimmunotherapy may impact future survival outcome remains uncertain [29]. Regarding this topic, La Mura et al. Twenty-five of the 69 HCV-positive subjects received antiviral therapy interferon and ribavirin following antineoplastic treatment, in order to eradicate HCV infection. Overall survival OS was slightly better in HCV-infected NHL patients treated with antiviral therapy compared with untreated, even if without statistically significance. Conversely, disease-free survival DFS was significantly improved in treated versus untreated patients. At multivariate analysis, the independent factors related to a better DFS in this series were antiviral therapy and indolent histology at the onset of lymphoma [39]. Antiviral treatment may be a strategy to reinforce the results of successful chemoimmunotherapy regimens, but future prospective studies are needed to further investigate this clinical issue. Of interest, a recent study has shown that HCV-infected patients who had received interferon therapy and had experienced a sustained virologic response had a hazard ratio of lymphomagenesis that was significantly lower than patients who had not received antiviral treatment [40]. These data suggest that antiviral treatment may also be efficacious in preventing lymphomagenesis in HCV-infected patients. Moreover, it should be of interest to investigate the impact of newer directly acting antiviral agents, such as protease inhibitors telaprevir and boceprevir [11 , 41 â€" 43], on the future prevalence and clinical outcome of B-NHL in patients with chronic HCV infection. While reactivation risk of hepatitis B virus HBV after chemoimmunotherapy is well recognized and prophylactic antiviral therapy to suppress HBV-DNA is widely recommended, the issue of HCV reactivation in lymphoma patients undergoing antineoplastic treatments is lesser understood [29 , 44]. However, a significant proportion of patients with HCV-positive NHL, when treated with conventional chemoimmunotherapy, may develop liver toxicity due to either direct cytotoxicity or increased drug toxicity from suboptimal drug metabolism [29 , 45]. The addition of rituximab to chemotherapy does not seem to impact significantly on liver toxicity [45]. HCV-RNA levels appear to increase during chemoimmunotherapy as a result of viral reactivation, but HCV-RNA levels subsequently decrease at 6 months posttreatment, often without major clinical consequences to most patients [44]. Nevertheless, it should also be noted that massive liver necrosis may occur in HCV-positive lymphoma patients on withdrawal of chemotherapy or reduction of corticosteroids, suggesting an immune-mediated mechanism of hepatic damage [44 , 46]. Without initial liver dysfunction, HCV-positive patients with NHL could experience a similar outcome compared with their HCV-negative counterparts, when treated with conventional chemoimmunotherapy [44 , 47]. A protective role of antiviral prophylaxis to suppress HCV replication during antineoplastic treatments has not yet been defined [29 , 44]. Prospective studies and longer followups are necessary to ascertain whether HCV-positive B-NHL patients have inferior outcome or whether there would be long term consequences of chemoimmunotherapy on the progression of liver disease [47]. Furthermore, hematologists and hepatologists should work closely together in order to optimize the management of HCV infection throughout lymphoma treatment and improve clinical outcome [29]. Nevertheless, limited information are so far available about the biological mechanisms of HCV-induced lymphoproliferation. Evidences from experimental studies suggest that several different mechanisms may be involved in HCV-mediated B-cell transformation [16 , 29 , 48]. Similarly to the association of Helicobacter pylori infection and gastric MALT lymphoma, the concept of chronic antigen stimulation leading to a monoclonal malignant proliferation may also be applied to HCV Figure 1 A [49 , 50]. Interestingly, HCV-associated B-NHL generally originate from germinal center GC or post-GC B-cells, suggesting that

lymphomagenesis occurs when B-cells experience somatic hypermutation and proliferate in response to an antigen [51 , 52]. These data indicated the role of a common antigenic epitope involved in the selection and in the expansion of the B-cell clone at the origin of neoplastic cells. The VH immunoglobulin segment is expressed in the restricted repertoire of fetal liver B lymphocytes and is thought to be involved in natural immunity. A productive VH rearrangement is present in 1. Similarly, in a reported case of an HCV-associated plasma cell leukemia, immunoblotting showed that the monoclonal IgG-kappa detected in the serum was directed against a viral protein, namely, the HCV core protein [59]. These and other studies suggest an indirect, antigen-driven lymphomagenetic role of HCV, with HCV-E2 protein recognized as one of the most important antigens involved in chronic B-lymphocyte stimulation [16 , 26 , 29]. Aâ€”D The different oncogenetic mechanisms are not mutually exclusive, but they may be integrated and cooperate in a multifactorial pathogenetic model of HCV-associated B-cell lymphoproliferation. This complex reduces the threshold for B-cell activation via the B-cell receptor by bridging antigen specific recognition and CDmediated complement recognition [60 , 61]. It was reported that engagement of CD81 on human B-cells by a combination of HCV E2 protein and anti-CD81 mAb leads to the proliferation of naive B-cells, and E2-CD81 interaction induces protein tyrosine phosphorylation and hypermutation of the immunoglobulin genes in B-cell lines [62]. In addition to direct effects on B-cells, engagement of CD81 on T-cells lowered the threshold for interleukin-2 production, resulting in strongly increased T-cell proliferation. This could lead to T-cell activation in response to suboptimal stimuli and bystander activation of B-cells [63]. Taken together, these results suggest that CD81 engagement on B- and T-cells may lead to direct or indirect activation [16]. The effects were dependent on E2-CD81 interaction on the cell surface, since CDsilenced Raji cells did not respond to both treatments. Of note, the effects were not associated with HCV replication in cells [65]. Hence, E2-CD81 engagement plays a role in activating B-cells, protecting B-cells from activation-induced cell death, and regulating immunological function. These latter mechanisms may contribute to the pathogenesis of HCV-associated B-cell lymphoproliferative disorders [65]. Moreover, the interaction between HCV-E2 and CD81 on B-cells has been shown to stimulate the enhanced expression of activation-induced cytidine deaminase AID and to induce double-strand DNA breaks in the IgVH gene locus, thereby contributing to a mutator phenotype that increases the risk of B-cell malignant transformation [66]. Another oncogenetic mechanism that has been proposed is the direct infection of B-cells by HCV Figure 1 C [16 , 29 , 67]. Nevertheless, although HCV has been detected in lymphocytes from HCV infected patients and patients with MC, only in a minority of cases RNA-negative strands, the HCV replicative intermediates suggestive of viral replication, were also detected in the cells [72 â€” 74]. Furthermore, Stamataki et al. These cells have been shown to express high levels of CD81 and to expand in HCV-infected liver [79]. Alternatively, B-cells may need another event, such as coinfection with another virus, namely, Epstein-Barr virus EBV , to become permissive for HCV infection and replication [16 , 80]. Neither HCV-RNA nor viral proteins have generally been detected in lymphomatous cells in vivo, with a few exceptions, for example a primary DLBCL of the liver, found to harbor viral nucleic acids by in situ hybridization and a mantle cell lymphoma case, from which a lymphoma cell line could be established in vitro [26 , 81 , 82]. Moreover, Sung et al. Further studies provided evidence that HCV replicates in various hematopoietic cell types, including peripheral dendritic cells, monocytes, and macrophages [84 â€” 86]. Overall, despite the evidence that HCV can infect B-cells, the results about its capacity to replicate in B-cells and other blood mononuclear cells and to induce direct malignant lymphoproliferation still appear highly conflicting [16 , 29]. Moreover, these mice showed increased levels of interleukin IL -2 and IL, as well as increased Bcl-2 expression, which promoted oncogenic transformation of lymphocytes. A recent study found that peripheral blood B-cells from patients with chronic HCV infection were infected and also had enhanced gene expression associated with B-NHL development when compared to healthy controls [88]. Furthermore, HCV has been found to induce high mutation frequency of cellular genes immunoglobulin heavy chain, Bcl-6, p53 and beta-catenin genes , in B-cell lines and PBMCs in vitro, by inducing double strand breaks and by activating error-prone-polymerases

and AID [89]. These mutations of cellular genes are amplified in HCV-associated B-NHL in vivo, suggesting that HCV-induced mutations in proto-oncogenes and tumor suppressor genes may lead to oncogenetic transformation of the infected B-cells. It has been proposed that HCV uses B-cells as reservoirs for persistent infection, which could result in the enhanced expression of lymphomagenesis-related genes, particularly AID, which is thought to be crucial for the initiation and progression of B-NHL [67]. Other studies suggested that the evolution from lymphoproliferation to malignancy may require a second transforming event such as the antiapoptotic Bcl-2 rearrangement. The t 14;18 translocation is indeed significantly associated with chronic HCV infection and particularly with MC [90 , 91]. Although the role of virus penetration and replication in B-cells has still to be fully clarified, several evidences suggest that the presence of HCV virus or HCV proteins in these cells represents an oncogenic stimulus [16 , 29]. The clinical evidence that antiviral therapy has a significant role in the treatment and prevention of some HCV-associated lymphoproliferative disorders, especially indolent B-NHL, further supports the existence of an etiopathogenetic link. The mechanisms exploited by HCV to induce B-cell lymphoproliferation differ from the classical mechanisms of herpesviral-induced lymphomagenesis, which require the maintenance of either EBV or human herpesvirus-8 genomes in the transformed B-cells as clonal episomes, together with the expression of an array of latent and, to a lesser extent, of lytic proteins [92]. Conflict of Interests The authors indicated that there are no potential conflicts of interests. View at Google Scholar F. Dal Maso and S. View at Google Scholar O. View at Google Scholar J.

Chapter 4 : Hepatitis C Virus Infection and Lymphoma

Persistent hepatitis C virus (HCV) infection is an etiological agent of chronic hepatitis that may evolve toward cirrhosis and hepatocarcinoma. In addition, HCV is associated with extrahepatic manifestations, especially lymphoproliferative disorders, including type II 'mixed' cryoglobulinemia (MC) [1] and non-Hodgkin lymphoma (NHL).

 Abstract Hepatitis C virus HCV has been recognized as a major cause of chronic liver diseases worldwide. Epidemiological data indicate an association between HCV chronic infection and the occurrence of B-cell NHL, suggesting that chronic HCV infection is associated at least in part with B-cell lymphomagenesis. In this paper, we aim to provide an overview of recent literature, including our own, to elucidate a possible role of HCV chronic infection in B-cell lymphomagenesis. HCV infection is a worldwide problem affecting nearly million people [2] and causes prolonged and persistent diseases in virus carriers, often leading to chronic hepatitis, cirrhosis, and hepatocellular carcinoma [3]. The pathogenic role of HCV in B-cell disorders has been suggested in reports wherein a clinical resolution of the B-cell dysfunctions, stated above, was observed after successful anti-HCV treatment using interferon IFN [8 â€” 10]. Based on such evidences, a possible role of B cells in HCV pathogenesis has been postulated but not yet conclusively demonstrated. The objective of this paper is to summarize recent literature focused on the possible involvement of HCV infection in B-cell lymphomagenesis, which could offer new insights into the role of B cells in the pathogenesis of HCV infection. HCV, as the name indicates, has been regarded as a hepatotropic virus. However, the possibility that HCV infects cells other than hepatocytes cannot be excluded. Further evidence suggested that HCV replicates in B cells. For example, Morsia et al. Around the same time, Pileri et al. This finding thus provided a rationale for the notion that HCV infects and replicates in B cells. Several years later, Gong et al. Their results are in agreement with an earlier study by Sansonno et al. Meanwhile, Januszkiewicz-Lewandowska et al. An array of evidence suggests that HCV replicates in various cell types of PBMC, including peripheral dendritic cells, monocytes, and macrophages [25 â€” 27]. A recent study by Kondo et al. Under these circumstances, a number of reports have indicated that HCV infects CDpositive lymphocytes, preferentially B cells [18 , 29 â€” 31]. Furthermore, Inokuchi et al. However, as predicted by a computer program named mfold, these nucleotide substitutions did not affect RNA secondary structure or thermodynamic stability of IRES region [34]. Recently, HCV variants observed in B cells showed poor translational activity in hepatocytes but not in B-cell lines, indicating that adaptive mutations had occurred in B cells [35]. However, our results do not support the concept of lymphotropism or B-tropism of HCV in patients with CHC [30] but instead are in good agreement with studies by Muller et al. Further investigation involving a large number of HCV patients would be necessary to support this conclusion. The role of B cells in the pathogenesis of HCV infection is examined in the next section. This evidence posed a logical question as to how HCV evades the innate antiviral immune responses in B cells. However, this important issue has so far not been formally investigated. Sensing mechanisms for invading viruses in host immune cells consist of toll-like-receptor TLR- mediated [36] as well as retinoic-acid-inducible-gene-I- RIG-I- mediated [37] pathways. The constitutive expression levels of both kinases were found to be markedly enhanced in CHC B cells. These results strongly suggest that HCV infection circumvents innate antiviral immune responses, that is, type I IFN production in B cells, and Figure 1 thus, takes advantage of B cells for persistent infection. Impaired innate antiviral immunity in B cells of patients with chronic hepatitis C. It can be assumed that, among B-cell subsets, memory B cells are the main reservoirs of HCV infection primarily because of their long lifespans. This strategy would be beneficial for HCV in securing sites for long-lasting infection. HCV infection of hepatocytes has long been considered an a priori assumption. However, this assumption does not necessarily mean that hepatocytes are the exclusive target of HCV infection. Lymphoid reservoirs of HCV infection could play a role in viral persistence [29 , 46

â€” 48]. Several maneuvers are employed for persistent infection of HCV [49]. Viral modulation is an effective strategy to escape host immune responses [50]. Another strategy is the suppression of the innate immunity of host by viral components. Regardless of the mechanisms, the infection and replication of HCV in peripheral B cells should be considered barriers to the treatment of patients with CHC with antiviral regimens. Based on the notion that peripheral B cells serve as reservoirs for persistent HCV infection and from a therapeutic perspective, it may be beneficial to eliminate peripheral B cells in patients with CHC by the administration of anti-B-cell antibodies, such as rituximab, along with combination therapy with peginterferon and ribavirin to eliminate circulating HCV in the blood, leading to a synergistic effect on HCV clearance in patients with CHC. Because HCV RNA genomic sequences are not able to integrate into the host genome, indirect mechanisms of malignant transformation should be considered. Furthermore, the occurrence of a subsequent transformation may lead to B-NHL. A number of epidemiological studies regarding the association between HCV infection and the occurrence of B-NHL have been carried out [5 , 7 , 62 â€” 65]. Geographic differences in HCV genotype have been thought to cause these discrepancies [66] although this remains controversial. Large-scale, population-based, well-controlled studies are necessary to reach a robust conclusion. It can be concluded that, at least in areas with a high prevalence of HCV carriage, HCV is an important risk factor for B-cell lymphomagenesis. In this paper, we propose a novel hypothesis that peripheral B cells serve as reservoirs for persistent HCV infection. We also suggest that long-lasting HCV infection in B cells may induce lymphoproliferative disorders that may eventually evolve into B-cell NHL, although little is known about the mechanism responsible for B-cell lymphomagenesis. In the remainder of this section, the possible mechanisms of B-NHL tumorigenesis induced by HCV infection will be discussed based on current knowledge of lymphomagenesis-related genes. Activation-induced cytidine deaminase AID is essential for somatic hypermutation SHM and class switch recombination of immunoglobulin genes in B cells [67 â€” 69]. This is because a malfunction in either of the two processes stated above is apparently responsible for chromosomal translocations and aberrant SHM, which are the two main causes of genetic lesions associated with B-NHL [70 , 71]. Several oncogenes have been demonstrated to be targets for SHM with immunoglobulin genes. In many cases, these anomalies activate the DNA damage response system that either allows DNA repair or eliminates the aberrant B-cell clones [72]. Failure of these repair systems may be a cause of B-cell malignancies. However, their study did not assess which cell population showed an enhancement of AID expression. The fact that this enhancement of AID expression is confined to the B-cell subset is extremely intriguing because several reports have demonstrated the augmented expression of AID in B-NHL [26 , 76 , 77]. Using an AID-deficient mouse model, Pasqualucci et al. They addressed the issue of errors in AID-mediated antigen receptor gene modification processes being the principal contributors to the pathogenesis of human B-NHL. Thus, it is tempting to hypothesize that the enhancement of AID in CHC B cells is at least partly responsible for the initiation of lymphomagenesis. In fact, several recent studies suggest that AID is deeply involved in tumorigenesis [80 â€” 84]. These findings suggest that inappropriate expression of AID acts as a DNA mutator that enhances genetic susceptibility to mutagenesis [86]. Overexpression of CCND1, which alters cell-cycle progression, is frequently observed in various tumors and may contribute to tumorigenesis [87 , 88], whereas CCND2 is known to be expressed at constitutively high levels in B-NHL [89]. Presumably, the enhanced expression of these genes in CHC B cells [32] may also correlate with B-cell lymphomagenesis. Recently, A20 has gained much attention as a novel tumor suppressor [97 , 98]. Other investigators have subsequently supported their findings [,]. Moreover, A20 also regulates antiviral signaling as well as programmed cell death [â€”]. Currently, the expression, biological activities, and mechanisms of action of A20 have been the focus of attention on a wide scale [ ]. Interestingly, Ngueyn et al. An intriguing possibility is that the A20 gene interacts with and is mutated by AID, the expression of which is dramatically enhanced in CHC B cells [32]. Conclusion In this paper, we summarized recent studies illuminating the possible role of HCV infection in B-cell lymphomagenesis. We proposed a hypothesis that HCV utilizes B cells as reservoirs for persistent infection, which could result in the enhanced expression of

lymphomagenesis-related genes, particularly AID, which is thought to be crucial for the initiation and progression of B-NHL Figure 2. Elimination of HCV in plasma by antiviral reagents as well as in peripheral B cells by specific antibodies would be beneficial for patients with CHC to achieve a complete viral clearance. Finally, although a positive association between HCV infection and B-NHL occurrence is still being debated [â€"], it is worthwhile to investigate the possible mechanisms by which B-cell lymphoproliferative disorders, which may evolve into B-NHL, are induced in patients with CHC. Role of HCV infection in B-cell lymphomagenesis, a hypothesis. Acknowledgments The authors thank Dr. Miho Suzuki and Dr. Kenji Ikebuchi for providing us with blood samples. View at Google Scholar V. La Civita et al. Di Liberto et al. La Vecchia, and S.

Chapter 5 : HCV Infection and B-Cell Lymphomagenesis

Hepatitis C virus infection among patients with non-Hodgkin's to hepatitis C virus (anti-HCV) while 1 patient (%) possible role of HCV in lymphomagenesis. Whereas a high.

Sorry, we are unable to provide the full text but you may find it at the following location s: Suggested articles Citations Akama F et al Hepatic mucosa-associated lymphoid tissue lymphoma and hepatocellular carcinoma in a patient with hepatitis B virus infection. Clinicopathological features of eight Korean cases of primary hepatic lymphoma. Effect of hepatitis C virus core protein on the molecular profiling of human B lymphocytes. Enhanced expression of lymphomagenesis-related genes in peripheral blood B cells of chronic hepatitis C patients. Establishment of B-cell lymphoma cell lines persistently infected with hepatitis C virus in vivo and in vitro. Extranodal lymphomas associated with hepatitis C virus infection. Hepatitis C virus induces a mutator phenotype: Higaki K et al Splenic large B-cell lymphoma in patients with hepatitis C virus infection. Itoh K et al Primary low-grade B-cell lymphoma of mucosa-associated lymphoid tissue MALT -type of the liver in a patient with hepatitis C virus infection. Nodular lymphoid hyperplasia of the liver with simultaneous focal nodular hyperplasia and hemangioma. Pathological classification of hepatic inflammatory pseudotumor with respect to IgG4-related disease. Persistent expression of full genome of hepatitis C virus in B cells induces spontaneous development of B-cell lymphomas in vivo. Primary biliary cirrhosis and hepatitis C virus infection. Primary hepatic diffuse large B cell lymphoma in a patient with chronic hepatitis C. Primary hepatic low-grade B-cell lymphoma of mucosa-associated lymphoid tissue MALT associated with primary biliary cirrhosis. Primary hepatic low-grade B-cell lymphoma of the mucosa-associated lymphoid tissue type. Primary hepatic lymphoma in hepatitis C. Primary hepatic lymphoma of mucosa-associated lymphoid tissue type. Primary hepatic marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type in a patient with primary biliary cirrhosis. Primary non-Hodgkin lymphoma of liver. Regression of splenic lymphoma with villous lymphocytes after treatment of hepatitis C virus infection. Report on a workshop convened to discuss the pathological and staging classifications of gastrointestinal tract lymphoma. Serumcryoglobulinemiaandchronichepatitis Cvirusdisease among Japanese patients. Splenic and nodal marginal zone lymphomas are indolent disorders at high hepatitis C virus seroprevalence with distinct presenting features but similar morphologic and phenotypic profiles. Stable remission after administration of rituximab in a patient with primary hepatic marginal zone B-cell lymphoma. WHO classification of tumours of haematopoietic and lymphoid tissues. WHO classification of tumours of the digestive system.

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Chapter 6 : Etiological factors in primary hepatic B-cell lymphoma - CORE

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The ted by the response to anti The authors have declared that no competing interests exist. Apart from its well known role as an etiological agent for non-A non A and non non-B viral hepatitis, there is growing evidence that hepatitis C virus is associated to B-cell B cell non-Hodgkin non lymphoma. The association between HCV and lymphoproliferative disorders has bee been recently postulated based on epidemiological data, biological studies and clinical observations. The causative role of HCV in those disorders has been further supported by the response to anti antiviral therapy. Despite a better understanding of pathophysiolo pathophysiological gical processes at stake leading from HCV infection to overt lymphoma, many issues still need to be further elucidated. Although HCV has been demonstrated to directly infect peripheral blood mononuclear cells both in vitro and, in some cases, in vivo, a strong rong body of evidence rather supports the hypothesis of an indirect transformation mechanism by which sustained antigenic stimulation leads from oligoclonal to monoclonal expansion and sometimes to lymphoma, probably through secondary oncogenic events. Here, Here, we review epidemiological and biological studies, as well as clinical data on antiviral therapy, linking HCV-infection HCV to B-cell cell non-Hodgkin non lymphoma. The virus lacks a reverse-transcriptase transcriptase and its genome encodes a single open reading frame for a large polyprotein, which is subsequently tly cleaved to Medit J Hemat Infect Dis ; 2 1 ;; Open Journal System structural and non-structural structural enzymatic component viral proteins. For more than a decade, evidence from either epidemiological studies, therapeutic approaches or biological data have emerged giving strong support to an etiological role of HCV in non-Hogkin lymphoma NHL development 1,2. Furthermore, HCVassociated NHL response to interferon IFN and ribavirin therapy in case of viral load decrease, previously described in several studies, also gave strong support for an etiopathological role of HCV in this kind of lymphoproliferative disorder. Although HCV is the major etiologic agent of non-A and non-B chronic hepatitis, it can present with a broad spectrum of extrahepatic manifestations. Among them, immune-related disorders have been described such as type II mixed-cryoglobulinemia MC , characterized by a monoclonal IgM with rheumatoid factor RF activity i. Among pathogenetic hypotheses, HCV lymphotropism has been studied but no direct transformation leading to an overt lymphoproliferative disorder has been clearly demonstrated. Conversely, strong evidence for an indirect role for HCV in inducing lymphoproliferative disorders has been given by recent findings. In this regard, association between HCV-infection, mixed cryoglobulinemia MC and NHL lent support to a multistep model in which HCV would induce a protracted stimulation of antigen-specific B-cell clones, leading to MC and in a subset of patients to overt lymphomas. Thus, cumulative evidence for a pathological link between HCV infection and lymphoma has emerged and will be reviewed in this paper. Early studies based on relatively small number of patients provided conflicting results and suggested a significant increased risk of B-NHL in HCVinfected patients only in high prevalence areas. This might be explained, at least in part, by a large difference in HCV prevalence itself which is lower in those countries , or by yet unknown environmental and genetic factors. It thus appears that there is a greater propensity to develop NHL in the setting of HCV infection, and that the risk is most dramatically evident in populations with high HCV prevalence. Besides, geographic variability worldwide may indicate additional important environmental factors influencing the strength of this relationship. Interestingly, during the same period following antiviral therapy, none of the patients who cleared the virus developed NHL whereas those who remained PCR positive had the same risk as not treated patients. However, despite these epidemiological and clinical evidences, the role of HCV in lymphomagenesis has remained elusive, and only recently have pathophysiological models started to emerge. If HCV infection has been inferred to be a factor in the development of NHL on the basis of case-control epidemiological studies as previously discussed, strong line of evidence also arose from response

of so called HCV-associated lymphoma to antiviral therapy. Hence, in , we reported the outcome of 9 patients who had splenic MZL with villous lymphocytes and HCV infection treated with interferon alfa-2b IFN alone or in combination with ribavirin. Histologically, the lymphoid marginal zone surrounding the follicular areas is expanded by neoplastic cells that have cytological and phenotypical features of marginal zone B cells. From a clinical point of view, the disease displays an indolent evolution with splenomegaly increasing over years and with a gradual progression of circulative malignant B cells. Of the 9 IFN-treated patients, 7 achieved a complete hematological remission, defined by the absence of abnormal lymphocytosis and the resolution of the splenomegaly, after HCV RNA load became undetectable. The remaining 2 patients experienced a partial or a complete response after addition of ribavirin and the loss of detectable HCV RNA. Conversely, none of 6 similarly treated HCVnegative SLVL patients responded to therapy thereby suggesting that the observed response rate was not due to the effect of interferon itself. Those results gave support to the hypothesis that HCV Medit J Hemat Infect Dis ; 2 1 ; Open Journal System might trigger, to some extent, clonal expansion and oncogenic events at least in a subgroup of indolent lymphomas patients. All patients were treated with alpha-IFN with 10 patients or without 8 patients ribavirin. Four patients had received prior therapy for SLVL including splenectomy or chemotherapy. Six patients received associated therapy for symptomatic MC steroids, cyclophosphamide or plasmapheresis. Two patients with major virological responses more than 2 log reduction in HCV RNA also achieved complete hematological remission, whereas the 2 patients with minor virological responses less than 2 log reduction in HCV RNA only achieved partial hematological responses i. Moreover, in one patient with a virological relapse, villous lymphocytosis reappeared, but re-initiation of antiviral therapy was associated with a second complete hematological remission following HCV RNA reduction. The mean time to treatment responses was approximately 4 months for both virological and hematological responses. Mean duration of antiviral treatment was 17 months. Responses were sustained, as the mean duration of hematological response was 62 months. Clinical manifestations of MC subsided in all patients after antiviral treatment. Interestingly, viral genotype did not seem to correlate with the response as 4 out of 7 patients presenting with HCV genotype 1, usually associated with poor responses, achieved a complete hematologic response. Of note, even for patients who exhibited a complete hematological remission, B-cell clone could still be detected in peripheral blood but clinical relapses did not occur if viremia remained negative. Blood smear showing a villous lymphocyte with conspicuous cytoplasmic villous protrusions from a patient with splenic lymphoma with villous lymphocytes SLVL. Although epidemiological studies and clinical data link NHL with HCV, underlying biological processes ultimately leading from infection to lymphoma are still poorly understood. Nevertheless, antigen-driven lymphoproliferation might be though of as being split into 2 distinct mechanisms. General models of lymphoid transformation by pathogens. Infectious agents such as Epstein-Barr virus directly target resting B-cell and establish latent infection. Transcription of viral latent genes with oncogenic potential leads to immortalization of infected B-cell and proliferation, normally kept in check by the immune system of the host. Under certain circumstances as immune deficiency or after additional oncogenic mutations, fully transformed EBVinfected B-cell might lead to malignant lymphoma. Persisting pathogens such as Helicobacter Pylori in chronic infection stimulate antigen-specific B-cell either directly or indirectly through T-cell help. Clonal expansion may develop in responding lymphocytes sometimes ultimately leading to frank lymphoproliferation. Several oncogenes have been described as targets for somatic hypermutation or translocations with immunoglobulin heavy-chains regions IgH. In most cases, these anomalies alarm the DNA damage response system that either allows for DNA repair or eliminates the aberrant B-cell clones. As regards to hepatitis C virus, few experimental data support the hypothesis of a direct transformation mechanism accounting for HCVassociated lymphomagenesis. In in vitro studies, CD81 has been shown to be an entry receptor for HCV and could be involved in infection of B cells by the virus. Similarly, frequent chromosomal polyploidy in peripheral blood mononuclear cells PBMC from HCV-positive patients was recently demonstrated, as well as in splenocytes from HCV core proteinexpressing transgenic mice, suggesting that HCV infection may inhibit the mitotic checkpoint. Therefore, identification of negative

strand RNA sequences in cells is indicative of active virus replication. So far, direct infection of the malignant clone has been described Figure 3. Hypothetical model of B-cell transformation by HCV. Interaction of E2 and CD81 on the cell surface induces expression of activation-induced deaminase AID and somatic hypermutations of immunoglobulin genes and potential proto-oncogenes. This mechanism may participate in Bcell transformation by HCV. B-cell transformation would not need to require direct infection of B-cells by HCV as this interaction takes place between extracellular E2 expressed on the virion and surface CD On the contrary, many studies support the role of HCV as an indirect transformation agent by chronically stimulating B-cell immunologic response and ultimately leading to overt lymphoma in some cases. Along with data on the response of lymphoma to therapy, antiviral treatment has been associated with disappearance of MC and in many cases of B-cell clones. Other recent data support a major role for HCV envelope glycoprotein E2 in indirect transformation.

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