Japanese Journal of Gastroenterology and Hepatology

Case Report ISSN 2435-1210 |Volume 6

Transformation of A Marginal Lymphoma in Hepatitis C Virus-Infected Patient After Clearance of HCV Viral Load

Martin P[1,3*], Verdu E[1], Romera I[2], Exposito M[1], Vicente Y[1], García D[1], Navarro B[2], Campos-Martin Y[4] and Bellas C[1,3]

[1]Department of Pathology, Hospital Universitario Puerta de Hierro-Majadahonda, Instituto de Investigacion Sanitaria Puerta de Hierro-Segovia de Arana, Madrid, Spain

[2]Department of Hematology, Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, Spain

[3]Centro de Investigacion Biomedica en Red de Cancer (CIBERONC), Madrid, Spain

[4]Department of Pathology, Hospital Virgen de la Salud, Toledo, Spain

[*]Corresponding author:

Paloma Martin,
Department of Pathology, Hospital Universitario Puertade Hierro-Majadahonda, Instituto de Investigacion Sanitaria Puerta de Hierro-Segovia de Arana, Majadahonda, Madrid 28222, Spain, Tel: +34 911917755;
Fax: +34 911917805,
E-mail: pmartin@idiphim.org

Received: 01 Mar 2021
Accepted: 22 Mar 2021
Published: 27 Mar 2021

Citation:

Martin P. Transformation of A Marginal Lymphoma in Hepatitis C Virus-Infected Patient After Clearance of HCV Viral Load. Japanese J Gstro Hepato. 2021; V6(6): 1-4

[&]Author Contribution:

Martin P, Verdu E, Romera I, Exposito M, Vicente Y, García D, Navarro B, Campos-Martin Y, Bellas C and these authors are contributed equally to this work.

Keywords:

Hepatitis C virus; Transformed diffuse large B cell lymphoma; MZL

1. Abstract

1.1. Introduction: Previous studies have shown an increased risk of B-cell lymphoproliferative disorders in patients with chronic hepatitis C virus (HCV) infection, mostly marginal zone lymphoma (MZL) and diffuse large B-cell lymphoma (DLBCL). Histologic transformation of low grade lymphoma to DLBCL is higher in HCV-infected patients.

1.2. Case presentation: We described the case of a 70-year-old man with a history of chronic HCV-associated cirrhosis who received antiviral therapy achieving a complete response. Eighteen months after virological response, multiple liver lesions were detected, and diagnosis of high-grade B cell lymphoma was done. Systemic staging study revealed bone marrow infiltration by MZL.

1.3. Discussion: We describe the development of DLBCL transformed from MZL in the context of clearance of chronic Hepatitis C infection.

2. Introduction

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) is the third commonest histological subtype and accounts for approximately 7-8% of all B-cell lymphoma [1]. Although the most common site of involvement is the stomach, non-gastric MALT lymphoma has been reported in many organs, which normally do not contain lymphoid tissue [2, 3, 4]. Primary hepatic lymphoma (PHL) is uncommon, represents 0.016% of all NHL and 0.4% of all extranodal lymphomas [5]. Although the cause of PHL is unknown, an association with viral etiology has been described. Persistent Hepatitis C virus (HCV) infection and the development of NHL has been reported [6], however the mechanisms by which lymphoma is induced by HCV are still limited. The HCV-induced transformation process of B-cell may occur in three different ways: persistent stimulation of B cell by the viral antigens with secondary proliferation, infection and persistent replication of HCV inside B-lymphocytes with oncogenic effects by viral proteins, and temporary intracellular virus replication with damage of B-cells [7].

The most frequent histological subtypes associated with chronic HCV infection are MZL (marginal zone lymphoma) including splenic and extranodal forms, DLBCL (diffuse large B cell lymphoma) and lymphoplasmacytic lymphoma [8, 9]. There was evidence that

DLBCL in HCV-positive patients are in a high proportion originated from low-grade lymphoma [10].

Our report documents the transformation of MZL to a high-grade DLBCL in chronic HCV infected patient after sustained clearance of HCV infection.

3. Case Presentation

We present the case of a 70-year-old man with a history of chronic HCV-associated cirrhosis, Child B7 with portal hypertension associated with splenomegaly. As complications to HCV infection, he developed several episodes of mixed cryoglobulinemia. He initially received Peg-IFN plus Ribavirin with relapse after stopping the treatment. He was started antiviral therapy with sofosbuvir-ledipasvir and completed 24 weeks of therapy achieving a complete response. The patient remained stable 18 months after successful therapy, but on routine abdominal ultrasound study, multiple liver lesions were detected.

Analysis of the peripheral blood revealed lymphopenia (0.76x10E3/microL) and thrombopenia (51.00x10E3/microL). Blood smear showed mature lymphocytes without morphological abnormalities. The laboratory tests showed the following: high serum total bilirubin (2.5mg/dL), high uric acid (8.5mg/dL), and high beta-2-microglobulin (5.0mg/L). Immunoglobulins and LDH levels were normal, and no serum monoclonal component was detected by electrophoresis. HCV viral load remained undetectable.

Liver biopsy was performed. Biopsy revealed liver tissue infiltrated focally by a neoplasm composed of medium/large lymphocytes with blastic appearance. These large cells were positive for CD20, CD10, BCL6, CD38, BCL2, P53 and MYC and negative for CD30, Cyclin D1, CD138 and MUM1. The proliferation index was close to 100%. FISH results showed *c-MYC* gene rearrangement without *BCL2* neither BCL6 translocation. The H&E histology along with the immunohistochemical profile confirmed the diagnosis of high-grade B cell lymphoma with *c-MYC* rearrangement (Figure 1).

Systemic staging revealed bone marrow infiltrated by small lymphocytes aggregates CD20 positive and CD5, CD10, BCL6 negative, which interstitial and paratrabecular localization. CD23 highlighted residual follicular dendritic cells in the center of the nodules suggesting colonization of the germinal center (Figure 2). These morphological and the immunophenotypical features were compatible with bone marrow involvement by MZL.

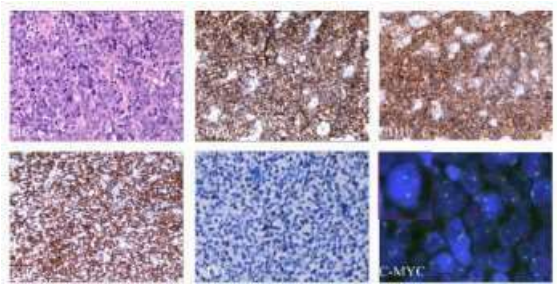

Figure 1: Liver biopsy showed medium/large lymphocytes with blastic appearance. Immunohistochemical staining was CD20 positive, CD10 positive, high Ki-67 proliferation index and MYC protein expression was positive in 50% of cells. FISH for *c-MYC* gene showed break apart pattern (red arrows).

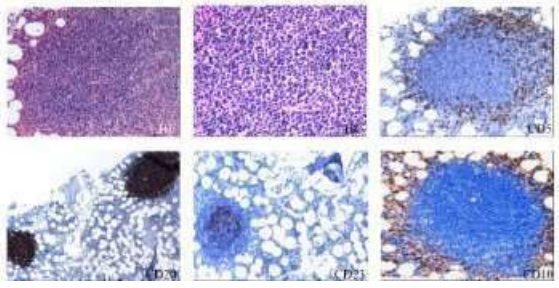

Figure 2: Bone marrow biopsy showed infiltration by small lymphocytes aggregates CD20 positive, CD5 negative, and CD10 negative. CD23 highlighted residual follicular dendritic cells in the center of the nodules suggesting colonization of the germinal center.

Heavy chain gene rearrangement using PCR assay (FR1, FR2 and FR3 regions) demonstrated the same clonal population in the bone marrow and liver samples. This suggests a high-grade B-cell lymphoma transformation from an HCV-associated MZL. Activating NOTCH-2 mutations were not found in both samples.

The patient underwent R-CHOP21 based regimen chemotherapy with radiological response at liver. Unfortunately, during the treatment the patient died suddenly. Postmortem study revealed rupture of a splenic artery aneurysm. Complete response using Cheson criteria [11] was achieved; there was no evidence of hepatic or spleen lymphoma infiltration.

4. Discussion

We presented a 70-year-old patient with 25year history of chronic HCV who developed a hepatic NHL. The link between HCV infection and the development of B-cell NHL has been reported especially in areas with high prevalence of this viral infection [9]. HCV lymphotropism and chronic antigenic stimulation are involved in B-lymphocyte expansion, as mixed cryoglobulinemia or monoclonal gammopathy of undetermined significance, which can progress to NHL. HCV-positive NHL usually occurs following a long period of infection and the more frequent entities are MZL and DLBCL.

Two forms of DLBCL presentations have been described in HCV positive patients; de novo DLBCL and transformation of MZL into aggressive DLBCL [12]. The case that we report showed MZL infiltration in bone marrow simultaneously with DLBCL in the liver, with presence of same clonal B-cell population in both localizations. These data suggest that the DLBCL could be originated from a MZL.

MZL have an indolent natural course and are slow to disseminate [13], but although uncommon, transformation to DLBCL may occur. Patients with MZL associated to HCV infection are more prone to transform into aggressive lymphoma than HCV negative cases [10, 12]. In the ANRSHC-13 lympho-C study nearly a third of DLBCL of the series were transformed from indolent lymphomas, mainly MZL [14].

NOTCH pathway is affected in approximately 30-40% of splenic MZL, including NOTCH-2 mutations, a key regulator of MZ devel- opment [15]. Identification of alterations on genes of the NOTCH pathway has been reported in 25% of cases HCV positive DLBCL patients [16] supporting the transformation of a previous low MZL. These cases have a worse clinical outcome with aggressive behavior and shorter overall survival. NOTCH-2 mutations in liver and bonemarrow were not found in our case.

In low-grade lymphomas HCV-positive cases, the antiviral therapy should be considered the treatment of choice [7], in analogy to the antibiotic therapy employed to treat MALT lymphoma associated with Helicobacter Pylori infection. Nevertheless, HCV-associated DLBCL patients should be treated with conventional immunochemotherapy schemes. The patient received R-CHOP21, with good response; unfortunately, he died for other causes than lymphoma. Interestingly, the development of lymphoma occurs in the context of clearance of chronic HCV infection. There are few reports [17, 18] to support the development of HCV-associated B-cell lymphoma after clearance of HCV viral load. Andrade et al. [17] hypothesize that HCV clearance may restore host T-cell and B-cell mediated immunity facilitating a previously suppressed lymphoid malignant clone to proliferate. One possible explanation is chronic antigen stimulation and clonal expansion with additional genetic alteration to malignant transformation. In our case, FISH study demonstrates *c-MYC* gene rearrangement in high grade lymphoma of the liver suggesting that deregulation of c-MYC could be the "second hit" in this case. C-MYC mediated repression of microRNA-34a, which is a potent tumor suppressor, and promotes high grade transformation in MALT lymphoma by deregulation of FoxP1 [19].

Little is known about development of lymphomas in the context of viral clearance of chronic HCV infection, further investigation is necessary to elucidate the role of antiviral therapy and the restoration of immunity in lymphomagenesis.

References

1. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H et al. WHO classification of Tumours of Haematopoietic and Lymphoid Tissues (Revised 4th edition).
2. Isaacson P, Wright DH. Extranodal malignant lymphoma arising from mucosa-associated lymphoid tissue. Cancer. 1984; 53: 2515-24.
3. Nart D, Ertan Y, Yilmaz F, Yuce G, Zeytunlu M, Kilic M et al. Primary hepatic marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type in a liver transplant patient with hepatitis B cirrhosis. Transplant Proc. 2005; 37: 4408-12.
4. Mizuno S, Isaji S, Tabata M, Uemoto S, Imai H, Shiraki K et al. Hepatic mucosa-associated lymphoid tissue (MALT) lymphoma associated with hepatitis C. J Hepatol. 2002; 37: 872-3.
5. Loddenkemper C, Longerich T. Lymphoma of the liver. In: Cavalli F, Stein H, Zucca E, editors. Extranodal Lymphomas, Pathology and Management. Abingdon, UK: CRC Press; 2008. 277-88.
6. Armand M, Besson C, Hermine O, Davi F. Hepatitis C virus - Associated marginal zone lymphoma. Best Pract Res Clin Haematol. 2017; 30: 41-49.
7. Pozzato G, Mazzaro C, Dal ML, Mauro E, Zorat F, Moratelli G et al. Hepatitis C virus and non-Hodgkin's lymphomas: Meta-analysis of epidemiology data and therapy options. World J Hepatol. 2016; 8: 107-116.
8. Nieters A, Kallinowski B, Brennan P, Ott M, Maynadie M, Benavente Y et al. Hepatitis C and risk of lymphoma: results of the European multicenter case-control study EPILYMPH. Gastroenterology. 2006; 131: 1879-86.
9. Vannata B, Arcaini L, Zucca E. Hepatitis C virus-associated B-cell non-Hodgkin's lymphomas: what do we know? Ther Adv Hematol. 2016; 7: 94-107.
10. Besson C, Canioni D, Lepage E, Pol S, Morel P, Lederlin P et al. Characteristics and outcome of diffuse large B-cell lymphoma in hepatitis C virus-positive patients in LNH 93 and LNH 98 Groupe d'Etude des Lymphomes de l'Adulte programs. J Clin Oncol. 2006; 24: 953-960.
11. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007; 25: 579-586.
12. Couronne L, Bachy E, Roulland S, Nadel B, Davi F, Armand M et al. From hepatitis C virus infection to B-cell lymphoma. Ann Oncol. 2018; 29: 92-100.
13. Huang W, Guo L, Liu H, Zheng B, Ying J, Lv N et al. C-MYC overexpression predicts aggressive transformation and a poor outcome in mucosa-associated lymphoid tissue lymphomas. Int J Clin Exp Pathol. 2014; 7: 5634-5644.

14. Michot JM, Canioni D, Driss H, Alric L, Cacoub P, Suarez F et al. Antiviral therapy is associated with a better survival in patients with hepatitis C virus and B-cell non-Hodgkin lymphomas, ANRS HC-13 lympho-C study. Am J Hematol. 2015; 90: 197-203.

15. Arcaini L, Rossi D, Lucioni M, Nicola M, Bruscaggin A, Fiaccadori V, et al. The NOTCH pathway is recurrently mutated in diffuse large B-cell lymphoma associated with hepatitis C virus infection. Haematologica. 2015; 100: 246-252.

16. Campos-Martin Y, Martinez N, Martinez-Lopez A, Cereceda L, Casado F, Algara P et al. Clinical and diagnostic relevance of NOTCH2- and KLF2-mutations in splenic marginal zone lymphoma. Haematologica. 2017; 102: e310-e312.

17. Andrade XA, Paz LH, Nassar M, Oramas DM, Fuentes HE, Kovarik P et al. Primary Liver Diffuse Large B-Cell Lymphoma following Complete Response for Hepatitis C Infection after Direct Antiviral Therapy. Acta Haematol. 2018; 139: 77-80.

18. Lin RJ, Moskovits T, Diefenbach CS, Hymes KB. Development of highly aggressive mantle cell lymphoma after sofosbuvir treatment of hepatitis C. Blood Cancer J. 2016; 6: e402.

19. Craig VJ, Cogliatti SB, Imig J, Renner C, Neuenschwander S, Rehrauer H et al. Myc-mediated repression of microRNA-34a promotes high-grade transformation of B-cell lymphoma by dysregulation of FoxP1. Blood. 2011; 117: 6227-36.