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Non-Hodgkin's Lymphoma as an Extrahepatic Manifestation after Achieving Sustained Virologic Response for Hepatitis C Viral Infection

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Abbreviations:
HCV: hepatitis C virus,
DAA: direct acting antivirals,
SVR: sustained virologic response,
BCL: B-cell non-Hodgkin's lymphoma,
DLBCL: diffuse and large B-cell non-Hodgkin's lymphoma,
CT: computed tomography,
MRI: magnetic resonance imaging,
LBNHL: large B cell non-Hodgkin's lymphoma,
NHL: Non-Hodgkin's lymphoma,
IFN: interferon.

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ABSTRACT

Hepatitis C virus is a hepatotropic and lymphotropic virus, triggering B-cells and promoting B lymphocyte proliferation. The association between chronic HCV infection and different lymphoproliferative disorders is well known. Antiviral therapy for HCV, including direct acting antivirals, has been proven as effective therapy of HCV-related lymphomas. So far, only few cases of lymphoma after HCV eradication have been reported in the literature. We report a series of 3 cases with HCV-related liver cirrhosis, two of them with sustained virologic response 12 weeks after direct acting antiviral therapy and one with spontaneous eradication of HCV infection, that were diagnosed with large B cell non-Hodgkin's lymphoma, that are still in remission actually, with a favorable evolution. Engaging the multidisciplinary team is tremendously important, since the diagnosis and management of those cases are successfully made by close collaboration between the gastroenterologist, hematologist, radiologist and pathologist, using imaging techniques, histopathological and immunohistochemical analysis. In the era of highly effective and safe direct acting antivirals, achieving sustained virologic response has been proven to prevent hepatic and extrahepatic malignant complications of chronic HCV infection, including lymphoma. However, recent reports showing the persistent risk for hepatic malignancy in some rare cases, demonstrate that HCV eradication is not the end point and this could be also in line with our cases of extrahepatic non-Hodgkin's lymphoma.

Key words: hepatitis C virus, lymphoma, direct acting antivirals, sustained virological response.

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INTRODUCTION

Hepatitis C virus (HCV) infection remains a global problem, even in the era of

direct acting antiviral (DAA) therapy, with very high sustained virologic response (SVR) rates. HCV is a hepatotropic and lymphotropic virus, chronic infection leading to chronic hepatitis, liver cirrhosis and hepatocellular carcinoma (1), but also to several extrahepatic manifestations, including lymphoproliferative disorders, such as B-cell non-Hodgkin's lymphoma (BCL), porphyria cutanea tarda or mixed cryoglobulinemia (2,3).

Several studies have demonstrated that HCV infection is an important factor in the development of different subtypes of BCL (4,5). In a study published by Torres HA et al, the most frequent HCV- related BCL are diffuse and large B-cell non-Hodgkin's lymphoma (DLBCL) (62%), followed by follicular lymphoma in 13% of cases and manta zone lymphoma (11%) (6). In some interventional studies, there was reported the regression of HCV-related non-Hodgkin's lymphoma after successful HCV eradication using antiviral therapy, but also the recurrence of lymphoma in case of non-response to antiviral therapy or recurrence of HCV infection (7,8). Three theories suggesting the implication of HCV in the lymphoma-genesis have been reported: a) viral antigens stimulate the lymphocyte receptors, with their consecutive proliferation; (b) the oncogenic effects, mediated by intracellular viral proteins, secondary to HCV replication in B lymphocytes and (c) the "hit and run" mechanism, meaning permanent destruction of B lymphocytes, caused by alterations in the tumor suppressor genes (9).

There are only few cases reported in the literature regarding HCV-related lymphoma after achieving SVR with interferon-free regimens (10,11), that can be attributed to the fact that viral eradication using DAA's can interfere with the immune system, favoring tumorigenesis (12).

CASE REPORT

The first case is a 66 years-old female, diagnosed with HCV–related liver cirrhosis since 2010, with no other co-morbidities, previously treated during 48 weeks in 2011 with peginterferon alpha-2a and Ribavirin, non-responder, with positive HCV ARN at the end of the treatment. She was treated during 12 weeks with Ombitasvir + Paritaprevir/Ritonavir and Dasabuvir + Ribavirin between December 2015 – February 2016 and achieved SVR with good evolution for a follow-up period of approximately 30 months. Patient was admitted in May 2018 with severe weight loss and bilateral supraclavicular lymphadenopathies, adhering to the deep plan, of firm consistency. A biopsy was performed from the mass previously mentioned and, after histopathological and immunohistochemical examination using specific markers for B lymphocyte, the diagnosis of diffuse and nodular large B cell non-Hodgkin's lymphoma (DLBCL) was established (*fig. 1*).

Abdominal ultrasound examination revealed multiple, large and conglomerated lymph nodes located intramesenteric and retroperitoneal, subsequently confirmed using computed tomography (CT) scan of the chest and abdomen (*fig. 2*).

The patient underwent chemotherapy with Rituximab, Ciclophosphamide, Vincristine and Dexamethasone (6 series), with good evolution and complete regression of the lymphoma.

The second patient is a 52 years-old patient, diagnosed in July 2017 with decompensated liver cirrhosis secondary to genotype 1b HCV infection, portal vein thrombosis and grade III esophageal varices, with 2 endoscopic prophylactic variceal ligations. The patient received Harvoni plus Ribavirin for 12 weeks between January 2018 – March 2018, achieving SVR 12 months later. During the follow-up, 12 weeks after SVR, an abdominal ultrasound was performed and multiple abdominal lymph nodes were detected, subsequently confirmed using abdominal magnetic resonance imaging (MRI) technique (*fig. 3*); in addition, a splenic nodule with malignant appearance on imaging was described.

A CT – guided biopsy from an abdominal lymph nodule was performed establishing the diagnosis of DLBCL, after histopathological and immunohistochemical examination (positive immunohistochemistry for CD20, CD 79a, Bcl6, CD10, and proliferation index of 55-60%)(*fig. 4*).

The patient started therapy with Rituximab, Vincristine, Ciclophosphamide, Doxorubicin and Dexamethasone in November 2018 and underwent 4 cycles, well tolerated.

The last case is a 68 years-old woman, diagnosed with chronic HCV infection in 1997, treated with Peginterferon alpha-2a and Ribavirin in 2000, respectively 2004 as relapser. In 2007 she was diagnosed with compensated liver cirrhosis secondary to HCV infection, with undetectable HCV ARN at that moment. The patient presented in August 2018 with marked fatigue and severe weight loss. The abdominal ultrasound noticed irregular liver margins, with multiple liver nodules, of inhomogeneous aspect, with different sizes, that were distributed mainly in the right lobe. A thoraco-abdominal CT scan and abdominal MRI were performed and were noted pulmonary metastases and multiple liver nodules with malignant aspect, with a splenic nodular lesion, abdominal lymph nodules and peritoneal carcinomatosis (*fig. 5*).

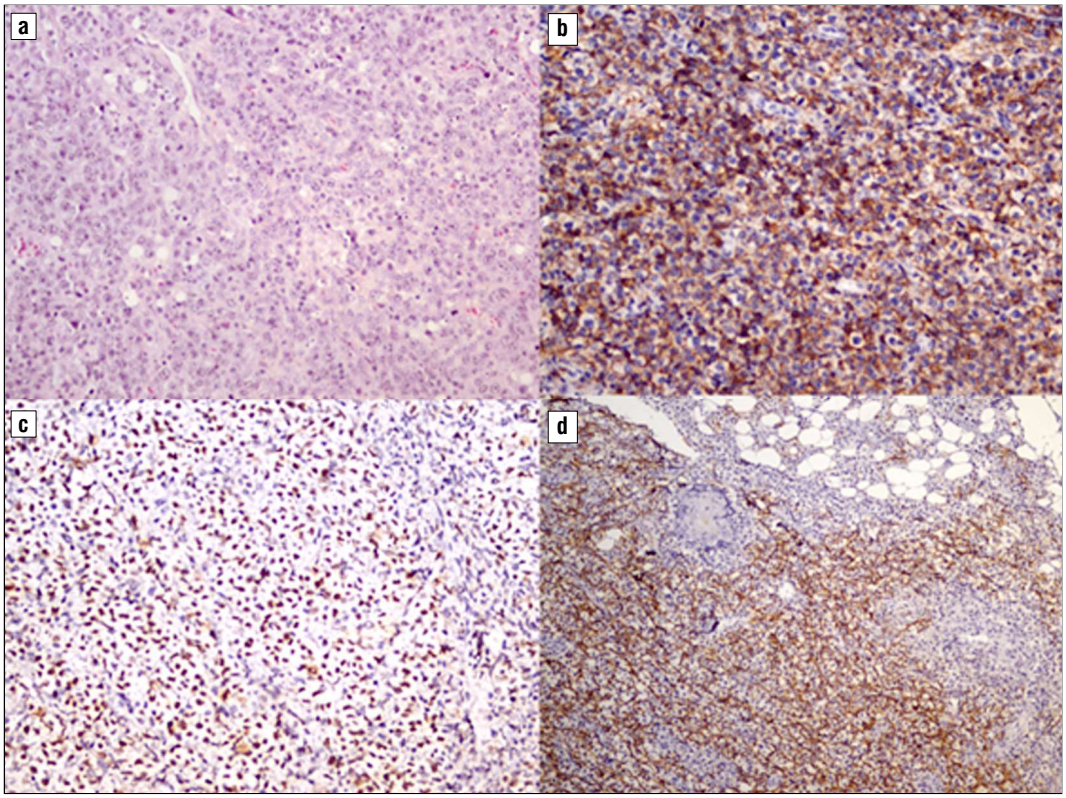

Figure 1 - Supraclavicular lymphadenopathy showing a lymphoid proliferation composed of large cells with abundant cytoplasm and large round-ovoid nucleai (a - Hematoxilin-eosin stain OBx 10). The phenotypic profile of the lymphoid cell shows extensive positivity for Bcl6 (nuclear staining)(b) and for CD20 (membranous staining)(c). (d) – Immunostain for CD23 highlights a diffuse follicular dendritic cell meshwork (disrupted follicular dendritic cell pattern).

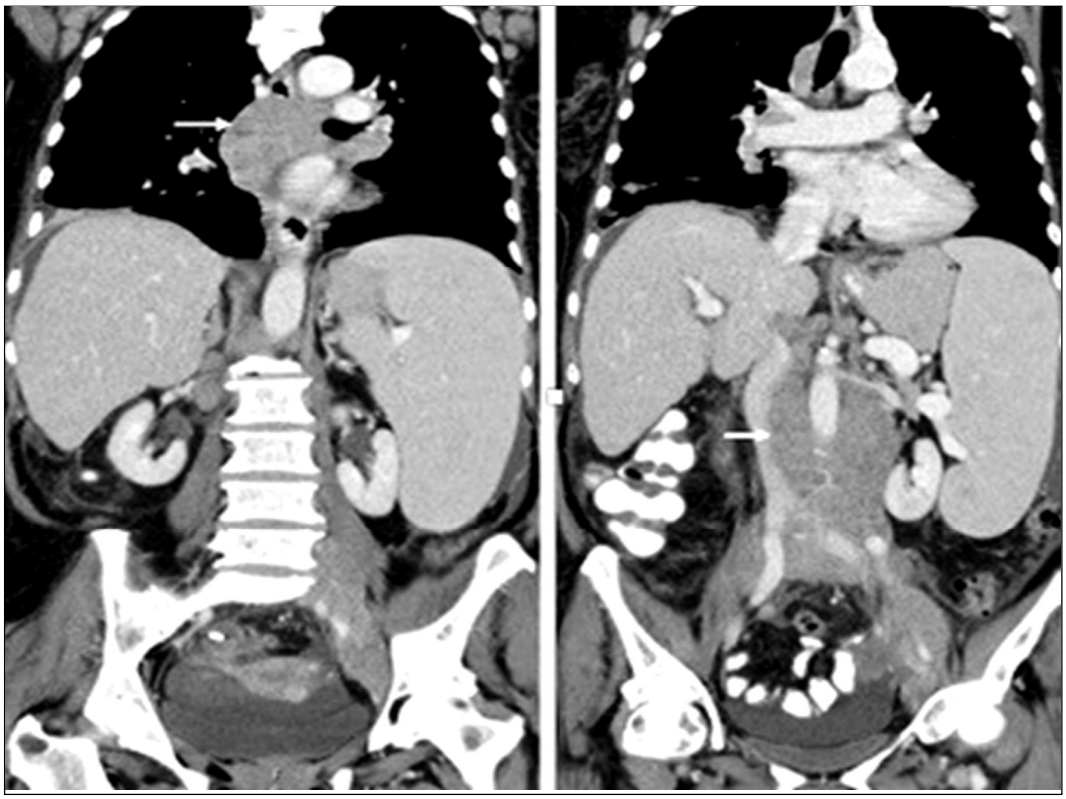

Figure 2 - Thoraco-abdominal CT scan with contrast enhancement showing multiple enlarged lymph nodes in the mediastinum and retroperitoneum along the inferior vena cava and abdominal aorta (white arrows).

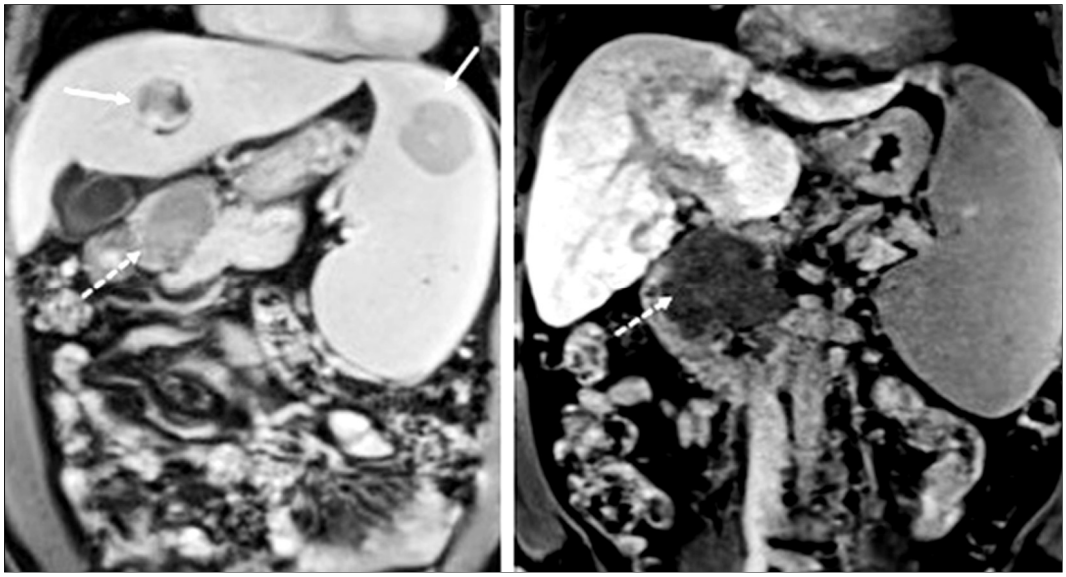

Figure 3 - Abdominal magnetic resonance imaging showing enlarged prepancreatic mass (dotted arrow), splenic and liver large nodules (white arrows).

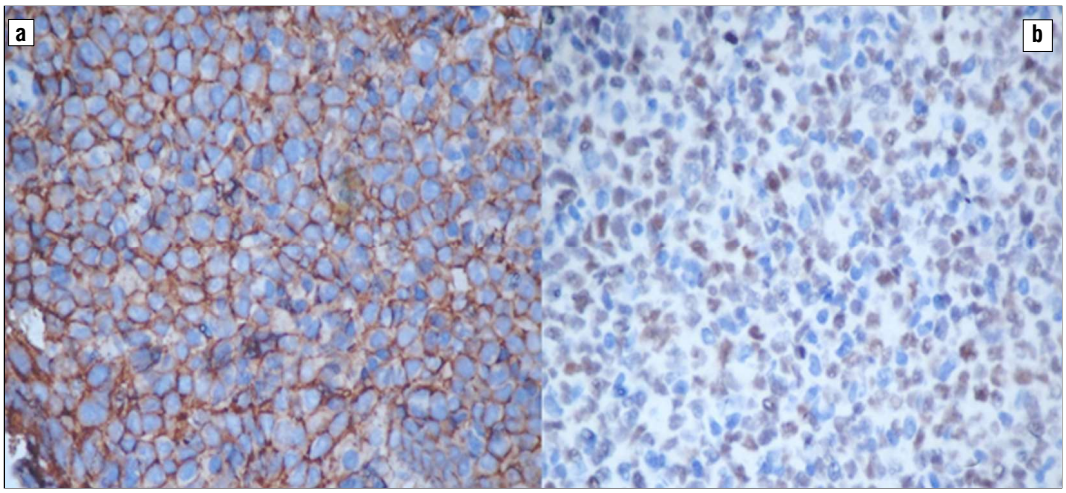

Figure 4 - Abdominal lymph node biopsy with diffuse large B cell lymphoma showing positive reaction for CD20 (a) of and Bcl6 (b) of tumour cells.

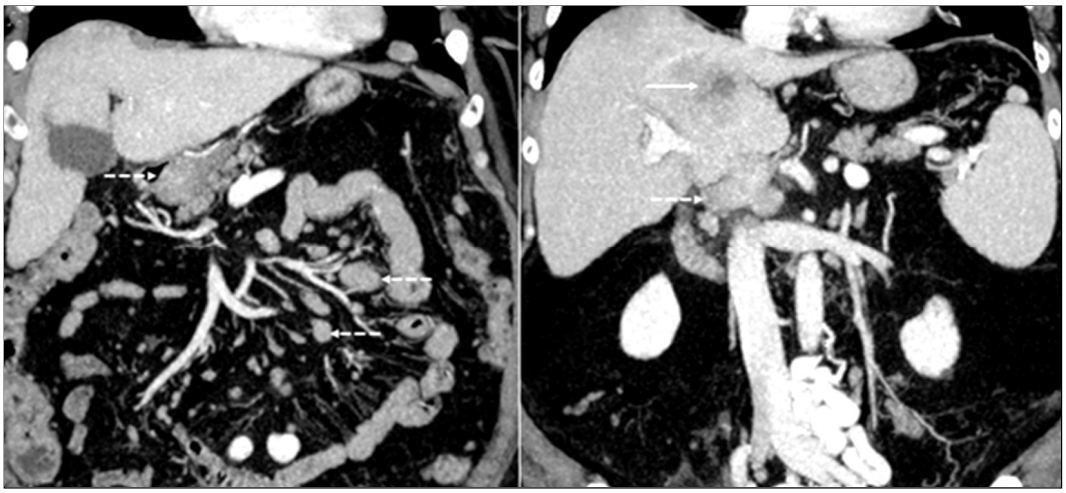

Figure 5 - Thoraco-abdominal CT scans – showing liver nodules (white arrow), multiple abdominal adenopathies (dotted arrows) and costal lesions.

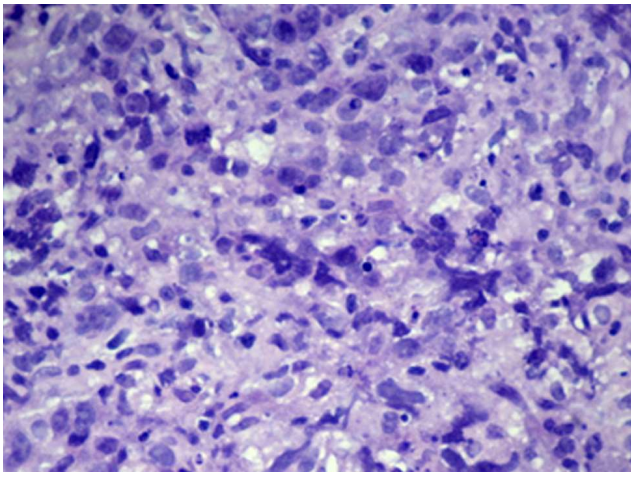

Figure 6 - Liver biopsy with infiltration by a lymphoid proliferation composed of medium to large pleomorphic cells with eosinophilic cytoplasm and vesicular nucleai (Hematoxilin-eosin stain, x40).

She underwent a percutaneous CT – guided liver biopsy and the histopathological and immunohistochemical diagnosis was hepatic infiltration of DLBCL (*fig. 6*).

A systemic chemotherapy was started using Rituximab, Doxorubicin, Ciclophosphamide, Vincristine and Dexamethasone, relatively well tolerated, with regression of the hepatic infiltration and secondary lesions.

RESULTS AND DISCUSSION

The association between HCV and different types of lymphoproliferative disorders is well known, epidemiological studies demonstrating an increased risk of non-Hodgkin's lymphoma (NHL) development in patients HCV infected, compared with patients without the infection (13-16). Several studies have reported regression of lymphoma after HCV eradication achieved with interferon (IFN) therapy (17-19), with improvement of overall survival (19-21).

A mechanism that can trigger the occurrence of lymphomas or hepatocellular carcinomas may be related to the rapidly reduce in hepatocyte inflammation after achieving SVR with interferon free regimens and the increase of lymphocytes, producing an imbalance, and thus favoring the tumorigenesis (9).

DAAs are potent drugs, with great efficacy and safety profiles, that improve long term prognosis in patients with HCV infection and can be curative in various cases of lymphoma (11). There are reported cases of HCV eradication with DAAs and complete remission of HCV-associated splenic or mantal zone lymphoma (22,23) and follicular lymphoma (24), without chemotherapy associated for the lymphoproliferative disorders.

While it was shown that HCV eradication is associated with lymphoma regression, occurrence of NHL after achieving SVR using IFN or IFN-free regimens is not a frequently seen scenario (25). E. Rodriguez de Santiago et al reported 2 cases of HCV-related lymphoma after DAAs in patients with advanced fibrosis, highlighting the importance of longstanding HCV infection advanced fibrosis, with patients in advanced stage being at higher risk for extrahepatic manifestations and the long – standing HCV infection (11). Some patients with chronic HCV may have irreversible injury to extrahepatic sites and although cured of HCV, patients may remain at risk for HCV related diseases, including HCV-associated primary and secondary malignancies, although at a lower risk compared to HCV positive patients similar to significant decreased risk of HCC development.

CONCLUSION

Achieving sustained virologic response using direct acting antiviral therapy for HCV infection, with viral clearance, represents the strategy to prevent the advance to higher stages of fibrosis and occurrence of different HCV – related hepatic and extrahepatic manifestations, but there are some new challenges, even after HCV eradication.

Conflicts of interest: None to declare.

Authors' contributions

M.G.: data collection, manuscript writing, S.I.: patient follow-up, patient management, critical review of the manuscript, I.G.L.: radiologic assessment, G.B.: histological and immunohistochemical assessment, D.C.: patient management and diagnosis, C.D. histological and immunohistochemical diagnosis, A.C.: histological and immunohistochemical assessment, A.B.: patient management and hematological treatment, C.G.: critical review of the manuscript, L.G.: patient diagnosis and follow-up, manuscript writing, critical review of the manuscript. All authors critically revised the manuscript, approved the final version to be published, and agree to be accountable for all aspects of the work.

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