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Case Report

CASE REPORT

Resolution of primary hepatic marginal zone lymphoma in a hepatitis C virus-infected patient treated with a direct-acting antiviral

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Abstract

The favorable impact of antiviral therapy on low-grade hepatitis C virus (HCV)-related non-Hodgkin lymphoma manifesting as marginal zone lymphoma (MZL) has been reported in some clinical studies. However, primary HCV-related marginal zone lymphomas (MZLs) confined to the liver have not been described in the literature nor have the resolution of liver lymphoma through anti-HCV eradication treatment. The authors report a genotype 1b HCV-positive patient with chronic hepatitis who exhibited lesions involving both hepatic lobes resembling hepatocellular carcinoma. Liver biopsy revealed an MZL of the liver. Antiviral treatment using sofosbuvir associated with simeprevir as unique treatment was started and resulted in complete haematological response. In HCV-related MZL isolated to the liver, antiviral treatment has led to the eradication of viral infection and a complete haematological response. Antiviral therapy should be considered as a first-line treatment for HCV-related primary MZLs of the liver.

INTRODUCTION

Hepatitis C virus (HCV) infection can lead to chronic liver disease and is associated with extrahepatic manifestations including B-cell non-Hodgkin lymphomas (B-NHLs). HCV-related B-NHLs more often manifest as marginal zone lymphomas (MZLs), diffuse large B-cell lymphomas (DLBCLs) or lymphoplasmacytic lymphomas [1]. In low-grade B-NHLs and, in particular MZLs, the favorable impact of antiviral therapy has been discussed in several clinical studies, although eradication of HCV infection was not always associated with B-NHL remission [2, 3]. On the contrary, in high-grade, HCV-related B-NHLs manifesting as DLBCLs, the first-line treatment is chemotherapy. We describe a unique case of HCV-related primary MZL of the liver with complete remission of lymphoma after antiviral treatment.

CASE REPORT

Ultrasonographic examination of an asymptomatic 62-year-old woman with chronic HCV genotype 1b infection revealed

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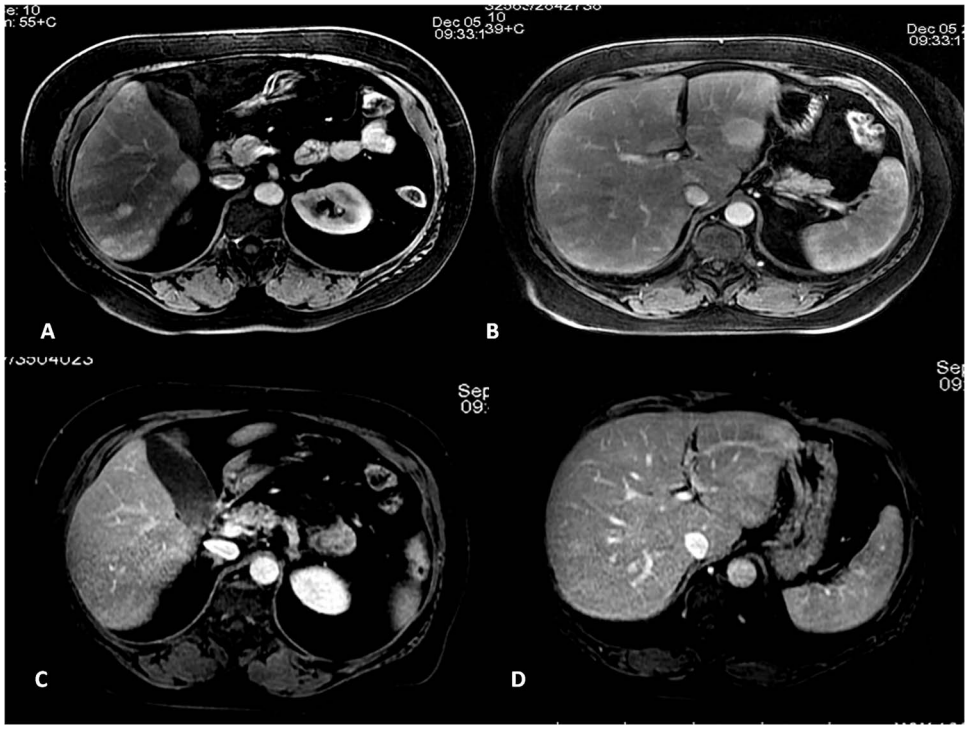

Figure 1: (A) Lava flex T1-weighted NMR after infusion of Gadobutrol 1.0 mmol/ml showing two lesions in liver segment VI; (B) lava flex T1-weighted NMR after infusion of Gadobutrol 1.0 mmol/ml showing a lesion in liver segment I III; (C) lava flex T1-weighted NMR after infusion of Gadobutrol 1.0 mmol/ml showing disappearance of the two lesions in liver segment VI; (D) lava flex T1-weighted NMR after infusion of Gadobutrol 1.0 mmol/ml showing disappearance of the lesion in liver segment III.

a hypoechogenic lesion in liver segment III. Active chronic liver disease was diagnosed 12 years previously based on liver biopsy that revealed a grade of 8 and stage 3 according to the Ishak staging system. Results of laboratory investigations were as follows: HCV RNA, 2530000 IU/ml; normal lactate dehydrogenase level (270 U/l [normal, 240–450 U/l]); haemoglobin, 12.9 g/dl; platelet count, 175.000/mm^3; white blood cell count, 4900/mm^2; aspartate aminotransferase, 40 U/l; alanine aminotransferase, 65 U/l; albumin, 4.1 g/dl and total bilirubin 1.0 mg/dl. Total body computed tomography (CT) with intravenous contrast revealed several nodular liver lesions with early arterial phase enhancement and slow washout with uncertain diagnosis. Magnetic resonance imaging (MRI) demonstrated hyperintensity on post-contrast T1-weighted images of the lesions and isointensity in the T2 phase (Fig. 1A and B). Positron emission tomography-CT (PET-CT) using 18F-fluorodeoxyglucose demonstrated only intense fluorodeoxyglucose uptake in different areas of the liver as a unique localization of the neoplasm. A liver biopsy was prompted by the uncertain behavior of the liver lesions. Microscopic examination of the liver biopsy revealed infiltration of typical centrocyte-like lymphoid cells and lymphoepithelial lesions in these small- to medium-size lymphocytes (Fig. 2A and B). Immunohistochemistry findings were positive for CD20, CD79a and BCL-2, and negative for CD3, CD5, CD10, CD43 and cyclin D1 (Fig. 2C and D). A diagnosis of stage IV liver MZL was made. Bone marrow biopsy did not reveal infiltration of lymphocytes. After haematology consultation, it was decided to administer antiviral therapy with sofosbuvir (NS5B inhibitor) associated with simeprevir (a protease inhibitor) for a duration of 12 weeks. Three months after the conclusion of antiviral treatment, HCV RNA was negative, thus confirming the eradication of HCV infection. MRI performed 6 and 12 months after antiviral therapy demonstrated complete resolution of the liver lesions (Fig. 1C and D). Currently, no liver lesions are apparent on MRI after 3 years of follow-up.

DISCUSSION

We report a case of primary hepatic lymphoma (PHL) due to HCV-related MZL. The phrase ‘primary liver lymphoma’ should be applied only to cases in which no other localization of NHLs is demonstrated; nevertheless, this entity remains controversial to some authors [4]. In our case, we did not find other sources of MZLs, given that PET-CT and bone marrow biopsy were negative for lymphoma localization at other sites. Although the World Health Organization classification system for lymphoma types does not report the classification ‘primary liver lymphoma’ in our case, we did not find other sources of MZLs [5]. The link between infectious agents and the development of MZLs has long been recognized, and the association between HCV and B-NHL has been firmly established in epidemiological studies [6]. However, the most convincing evidence supporting a causal relationship between HCV infection and MZLs in particular was the phenomenon of lymphoma regression after HCV eradication regardless of the antiviral treatment administered [2, 3]. It has been demonstrated that the HCV envelope glycoprotein E2 can interact with a specific B cell receptor associated with the CD19/CD21/CD81 complex. This interaction lowers the threshold for B cell activation and induces the proliferation of benign B cells. However, prolonged exposure to stimuli may render B cells to be at risk for additional events leading to malignant transformation. Antiviral treatment to eradicate HCV infection appears to halt these mechanisms of lymphomagenesis. In the National Comprehensive Cancer Network guidelines, version 1.2019, and, according to the American Association for the Study of Liver

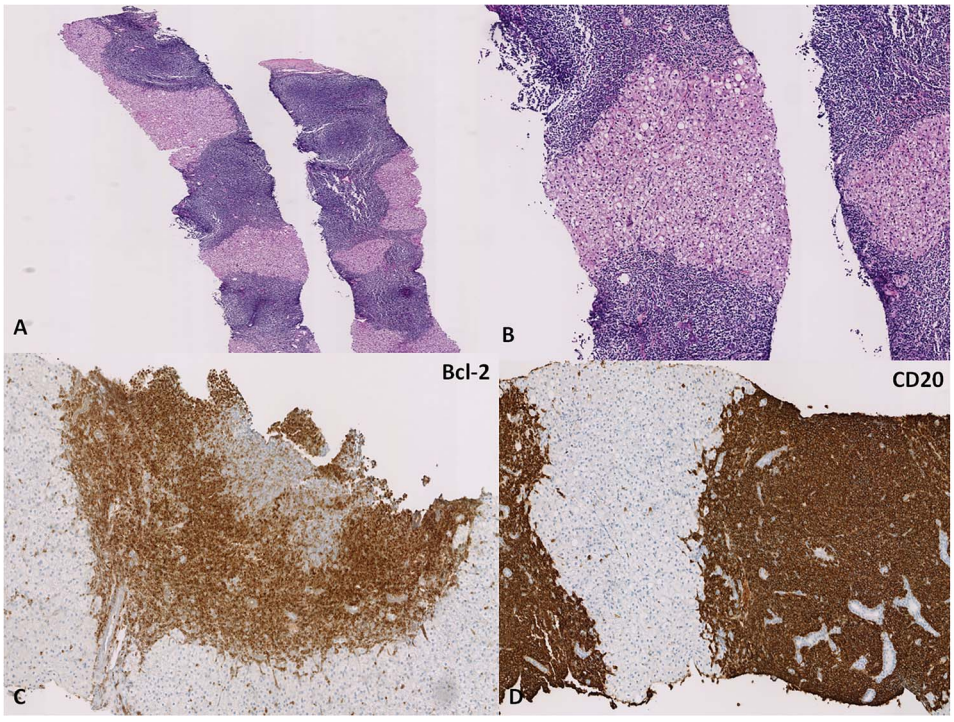

Figure 2: (A) An infiltration of small round to cleaved lymphocytes with germinal centers in the specimen; hematoxylin and eosin × 100, (B) hematoxylin and eosin × 400; (C) staining with immunohistochemical and expression of bcl-2 (×200); (D) staining with immunohistochemical and expression of CD20 (original magnification × 200).

Diseases, combined therapy with direct-acting antivirals should be considered in asymptomatic patients with HCV infection because it can result in regression of lymphoma in some cases [7, 8].

PHL is a very rare malignancy and accounts for only ~0.016% of all cases of non-Hodgkin's lymphoma and, among PHLs, a primary low-grade lymphoma of mucosa-associated lymphoid tissue type is extremely rare [9]. To our knowledge, only one case of HCV-related MZL in the liver has been reported in the literature [10]. In the case described here, the Authors did not attempt to confirm that the liver lymphoma was primary and baseline PET-CT was not performed. Furthermore, antiviral treatment was not effective in inducing regression of the hepatic lesions. We believe that the term 'PHL' must be considered in future B-NHL classifications.

In our case, the liver lesions appeared hypointense on T1-weighted images and isointense on T2-weighted images. After contrast administration, the lesions appeared hyperintense in the arterial phase without a clear washout in the portal and late venous phase. This behavior rendered the diagnosis of hepatocellular carcinoma uncertain. For these reasons, liver biopsy of the hepatic lesions was performed to differentiate hepatocellular carcinoma from other causes of liver masses.

In conclusion, we describe the first case of HCV-related MZLs isolated to the liver. This is a unique entity and should be suspected in HCV-infected patients exhibiting liver lesions with uncertain behavior without other demonstrable lymphoma localization. In our case, first treating the HCV infection appeared to be effective in determining a complete haematological response, and HCV treatment should be considered as first-line therapy. Chemotherapy must be reserved only for patients who do not respond to antiviral therapy.

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None.

CONFLICT OF INTEREST

No conflicts of interest are declared by the Authors.

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ETHICAL APPROVAL

No ethical approval is required.

CONSENT

Informed consent was obtained from the patient.

GUARANTOR

Adriano Pellicelli.

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