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To the editor:

Regression of an HCV-associated disseminated marginal zone lymphoma under IFN-free antiviral treatment

Hepatitis C virus (HCV) is prevalent in B-cell–associated lymphomas, including marginal zone and diffuse large B-cell lymphomas.[1] A stepwise model of lymphomagenesis induced by chronic antigenic stimulation and/or a direct pro-oncogenic effect of intracellular HCV proteins is a possible mechanism.[2] Interferon-based HCV treatment may induce remission and improve prognosis of HCV-associated lymphomas.[3] Whether these effects are due to HCV clearance or to an antiproliferative effect of interferon remains unknown. We describe a patient with a complete hematologic response of an HCV-associated disseminated marginal zone lymphoma (MZL) to an interferon-free anti-HCV treatment.

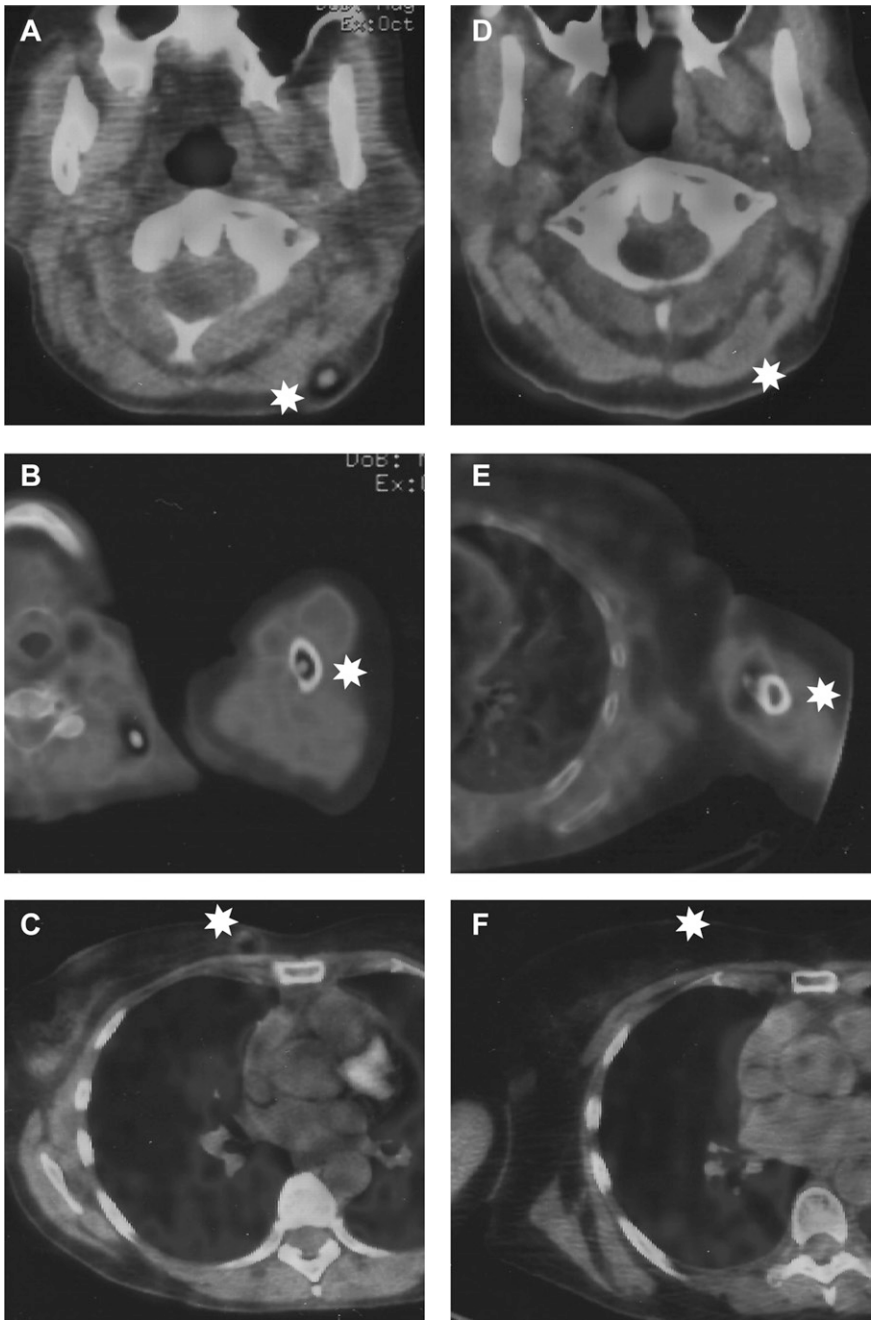

Figure 1. Representative pictures from the positron emission tomography scanner before and after interferon-free anti-HCV treatment. Left panels: photos before antiviral treatment of (A) infiltrated cervical lymph node, (B) left humeral shaft lesion, and (C) right breast lesion. Right panels: photos after sustained virologic response of (D) same cervical area, (E) left humeral shaft, and (F) right breast. White stars indicate the localization of the lymphoma.

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A 57-year-old woman presented in June 2013 with a right breast swelling. She had received anti-D immunoglobulins in 1984. Alanine and aspartate transaminase levels were 4 and 1.5 times above the normal range, respectively. Anti-HCV antibodies and HCV RNA (genotype 3a) were detected. The patient tested negative for hepatitis B surface antigen and anti-HIV antibodies. There were no direct or indirect signs of cirrhosis. Type III mixed cryoglobulinemia and rheumatoid factor were detected.

A biopsy specimen of the breast revealed an extranodal MZL. The staging evaluation revealed cervical lymphatic, breast, and left humeral shaft involvement without bone marrow infiltration with histologic infiltrate of small-size lymphoid cells with irregular nuclei and scattered lymphoid blasts. The lymphoma cells were $CD20^{+}$, $CD79a^{+}$, $BCL2^{+}$, $CD5^{-}$, $CD3^{-}$, $CD10^{-}$, $BCL6^{-}$, and cyclin $D1^{-}$. Given the putative causal link with HCV infection and the indolent course of the lymphoma, we chose to initiate an antiviral treatment aiming for a possible hemato-oncologic improvement associated with HCV clearance. During March 2014, an interferon-free antiviral treatment combining sofosbuvir (400 mg per day) and ribavirin (1000 mg per day) was started. Radiotherapy on the humeral shaft was conducted for a biopsy-induced pathologic fracture.

Within 2 weeks of treatment, the liver tests returned to normal and HCV RNA was undetectable in the serum. We replaced ribavirin with daclatasvir at week 4 of treatment and conducted a 12-week therapy of sofosbuvir and daclatasvir. Twelve weeks after the end of treatment, HCV RNA remained undetectable in the serum, defining a sustained virologic response. During the course of treatment, we observed a complete clinical and radiologic regression of breast, cervical ganglionic, and humeral shaft lesions, and the patient remained in complete remission 6 months after the end of antiviral treatment (Figure 1).

This clinical case is the first report of the efficacy of direct-acting antivirals in inducing remission of an HCV-associated disseminated MZL, and it highlights the causal relationship between HCV and MZL, given the rapid regression of lymphoma that was observed in parallel with HCV clearance under an interferon-free anti-HCV treatment.

Chronic HCV infection is a risk factor for B-cell non-Hodgkin lymphomas.[1] HCV replication associated with rheumatoid factor and/or mixed cryoglobulinemia production is believed to drive B-cell proliferation either by chronic antigenic stimulation or by pro-oncogenic activation by intracellular replication and synthesis of viral proteins.[2] The hematologic benefit of HCV clearance was first demonstrated with interferon-based antiviral treatments in villous splenic lymphoma.[4] Moreover, interferon-based antiviral treatment has been shown to improve the prognosis of HCV patients with B-cell lymphomas.[3] The underlying mechanism is still debated, with a potential antiviral and/or antiproliferative effect of interferon.

Our observation supports a direct HCV-mediated antigenic stimulation and/or a pro-oncogenic stimulation of B cells in the genesis of MZL. This is supported by a recent report of a splenic MZL regression after HCV clearance under interferon-free therapy.[5] The hematologic effect of HCV treatment seems related to the exclusive benefit of the control of HCV replication.

Research should be conducted to better define the indications of an interferon-free regimen as first-line therapy for HCV-associated lymphomas.

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Contribution: P.S. and C.K. collected patient data and wrote the manuscript; P.B. and S.P. reviewed the manuscript; and V.M. reviewed and edited the manuscript.

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