Case Reports in Gastroenterology

Case Rep Gastroenterol 2019;13:336–341

DOI: 10.1159/000501546
Published online: July 26, 2019

Single Case

Rapid Regression of B-Cell Non-Hodgkin's Lymphoma after Eradication of Hepatitis C Virus by Direct Antiviral Agents

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Keywords

Non-Hodgkin's lymphoma · Marginal zone B-cell lymphoma · Hepatitis C virus · Direct-acting antivirals · Sustained virologic response

Abstract

A 47-year-old woman visited Tokai University Hospital complaining of left cervical lymph node swelling in 2007. The laboratory data were almost normal except for slight anemia (Hgb 10.5 g/dL), elevation of serum soluble interleukin (IL)-2 receptor levels (645 U/mL [normal range 220–530 U/mL]), and positive hepatitis C virus (HCV) antibody. Serum transaminase and lactated dehydrogenase levels were normal. Contrast-enhanced computed tomography (CT) showed lymph node swelling with a diameter of 3 cm at the left supraclavicular fossa and mild splenomegaly, and ^{18}F-fluorodeoxyglucose positron emission tomography with CT (FDG-PET/CT) revealed abnormal uptake in the left supraclavicular fossa. The patient was diagnosed as having indolent nodal marginal zone B-cell lymphoma by lymph node biopsy. After 9 years with no progression of lymphoma, the patient received 12-week ledipasvir/sofosbuvir therapy for HCV infection and achieved sustained virologic response without any adverse effects. The left supraclavicular mass disappeared in the FDG-PET/CT performed 5 months after antiviral

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therapy indicating complete response. The serum soluble IL-2 receptor concentration decreased to 244 U/mL. Thereafter, her lymphoma was in remission for 3 years.

Introduction

Chronic hepatitis C virus (HCV) infection is a global health problem and more than 170 million people are infected with HCV worldwide [1]. Chronic HCV infection is not only a major cause of liver cirrhosis and hepatocellular carcinoma (HCC), but is also associated with several extrahepatic manifestations including mixed cryoglobulinemia, chronic kidney diseases, type 2 diabetes, B-cell non-Hodgkin's lymphoma (NHL), lichen planus, Sjögren's syndrome, porphyria cutanea tarda, rheumatoid-like arthritis, and depression [2].

Interferon (IFN)-based therapy had been the mainstay of the anti-HCV treatment for more than 20 years. Recently introduced IFN-free direct-acting antivirals (DAA) have higher efficacy in achieving sustained virologic response (SVR) than IFN-based regimens and are now being increasingly used. Several lines of evidence have demonstrated that SVR after antiviral therapy decreases the risk of HCC occurrence [3]. The SVR induced either by IFN-based regimens [4] or by DAA [5] reduced HCC risk by 70% or higher. Antiviral therapy is also expected to improve extrahepatic manifestations. Especially DAA are preferable due to the favorable tolerability and lack of immune-stimulatory properties. HCV infection is documented in most of the patients with mixed cryoglobulinemia, a clonal B-cell disorder causing systemic vasculitis. Eradication of HCV resulted in disappearance of cryoglobulin in approximately 50% [6]. Although not stronger than mixed cryoglobulinemia, the association between HCV infection and NHL is documented. In the countries with high HCV prevalence, ~10% of NHL patients are infected with HCV [7]. Complete remission of lymphoma by IFN-based regimens was documented [8] but it had been unclear whether lymphoma regression was induced by HCV clearance or IFN's antiproliferative effects. The former turned out to be correct because Arcaini et al. [9] reported that sofosbuvir-based DAA therapy resulted in high rate of response (73%) in 46 patients with indolent NHL. However, documentation of a case with lymphoma regression after DAA therapy is still scanty. We report here a patient whose indolent NHL rapidly disappeared after HCV eradication by DAA therapy.

Case Report

A 47-year-old woman visited Tokai University Hospital complaining of left cervical lymph node swelling in 2007. When she donated blood at the age of 30 years, she noticed that she was infected with HCV but did not receive antiviral therapy. She had no history of blood transfusion. She did not consume alcohol and was a nonsmoker. Physical examination was as follows: performance status: 0, height: 156 cm, weight: 51 kg, body temperature: 36.8°C, blood pressure: 101/67 mm Hg, and pulse rate: 80/min. The left cervical and supraclavicular lymph nodes were palpable, whereas liver and spleen were not palpable. The laboratory data were almost normal except for slight anemia (Hgb 10.5 g/dL), elevation of serum soluble interleukin (IL)-2 receptor levels (645 U/mL [normal range: 220–530 U/mL]), and positive HCV antibody. Serum aspartate transaminase (AST), alanine transaminase (ALT) and lactated dehydrogenase levels were normal. Contrast-enhanced computed tomography (CT) showed lymph nodes swelling with a diameter of 3 cm at the left supraclavicular fossa and mild

splenomegaly, and ^{18}F-fluorodeoxyglucose positron emission tomography with CT (FDG-PET/CT) revealed abnormal uptake in the left supraclavicular fossa (Fig. 1). The biopsy from this lymph node revealed the existence of diffuse proliferating monocytoid B cells with pale cytoplasm and round/irregular nuclei (Fig. 2a). These cells were immunohistochemically positive for CD20 (Fig. 2b) and BCL-2, and negative for CD3, CD5, CD10, BCL-6, MUM-1, and cyclin D1. Infiltrating plasma cells were kappa type dominant (Fig. 2c, d). Finally, she was diagnosed as nodal marginal zone B-cell lymphoma. She was followed up without treatment, and the lymph node swelling did not grow for 9 years. In 2016, the patient was referred to our Department for HCV treatment. Serum AST and ALT were still normal. HCV genotype was 1b and serum viral load was 7.0 logIU/mL. She received 12-week ledipasvir/sofosbuvir therapy and achieved SVR without any adverse effects. The left supraclavicular mass disappeared on the FDG-PET/CT performed 5 months after the end of DAA therapy (Fig. 1) indicating complete response. The serum soluble IL-2 receptor concentration declined to 244 U/mL. Thereafter, her lymphoma was in remission for 3 years.

Discussion

The patient we report on achieved SVR with 12-week ledipasvir/sofosbuvir treatment without adverse effects. DAA therapy is very effective in eradicating HCV with an SVR rate of >95% [10]. Another important advantage over IFN-based regimens is excellent tolerability that allows very ill patients to receive antiviral treatment. Therefore, DAA therapy is expected not only to reduce the risk of liver cirrhosis and HCC, but also to improve HCV-related extrahepatic manifestations [3].

In the present case, the left supraclavicular mass disappeared rapidly after DAA therapy. The mechanisms in which HCV infection causes NHL in the limited number of patients remain unknown, but a multistep theory of lymphomagenesis has been proposed [11, 12]. According to this hypothesis, chronic antigenic stimulation via HCV replication leads to B-cell proliferation and subsequent development of mixed cryoglobulinemia. In some patients, continuous stimulation generates indolent low-grade NHL. As the final step, low-grade NHL transforms into high-grade NHL such as diffuse large B-cell lymphoma (DLBCL) by the accumulation of additional mutations and genetic alterations. In this stage, lymphoma grows without antigen stimulation and treatment requires general chemotherapy. The present case suffered from nodal marginal zone B-cell lymphoma, which accounts for approximately 12% of all B-cell lymphoma [13]. This type of lymphoma is frequently associated with HCV infection; ~15% of patients were serologically positive for HCV in areas where HCV prevalence was high [14]. These patients with HCV infection like our case are recommended to receive DAA therapy [12]. In contrast, the impact of HCV eradication on HCV-associated DLBCL remains unclear. Recently, Persico et al. [15] studied the effect of DAA therapy on the clinical course of HCV-associated DLBCL. Twenty patients who received DAA therapy during chemotherapy had significantly higher disease-free survival than historical cohort. Therefore, combination of DAA and chemotherapy may be a good option for this entity of lymphoma.

Our patient has been in remission for 3 years after regression of lymphoma. Although risk of relapse may be lowered under the lack of antigenic stimulation, evidence concerning relapse after HCV eradication is insufficient. We think that the case should be monitored every 6 months.

Statement of Ethics

The authors have no ethical conflicts to disclose. We obtained written informed consent from the patient. This study was approved by the Tokai University Institutional Review Board.

Disclosure Statement

The authors have no funding or conflicts of interest to disclose.

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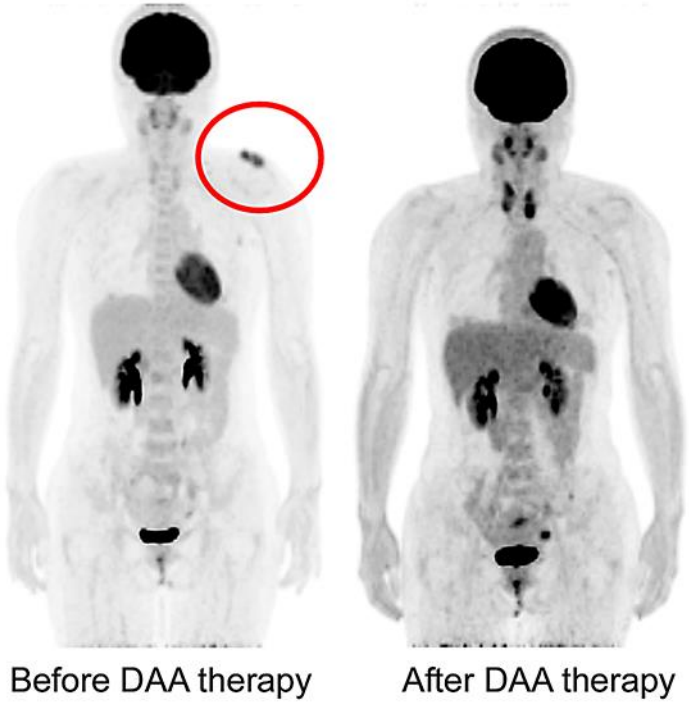

Fig. 1. ^{18}F-fluorodeoxyglucose positron emission tomography with computed tomography (FDG-PET/CT) images showing abnormal uptake in the left supraclavicular fossa before DAA therapy (circle) and its disappearance after DAA therapy.

DOI: 10.1159/000501546

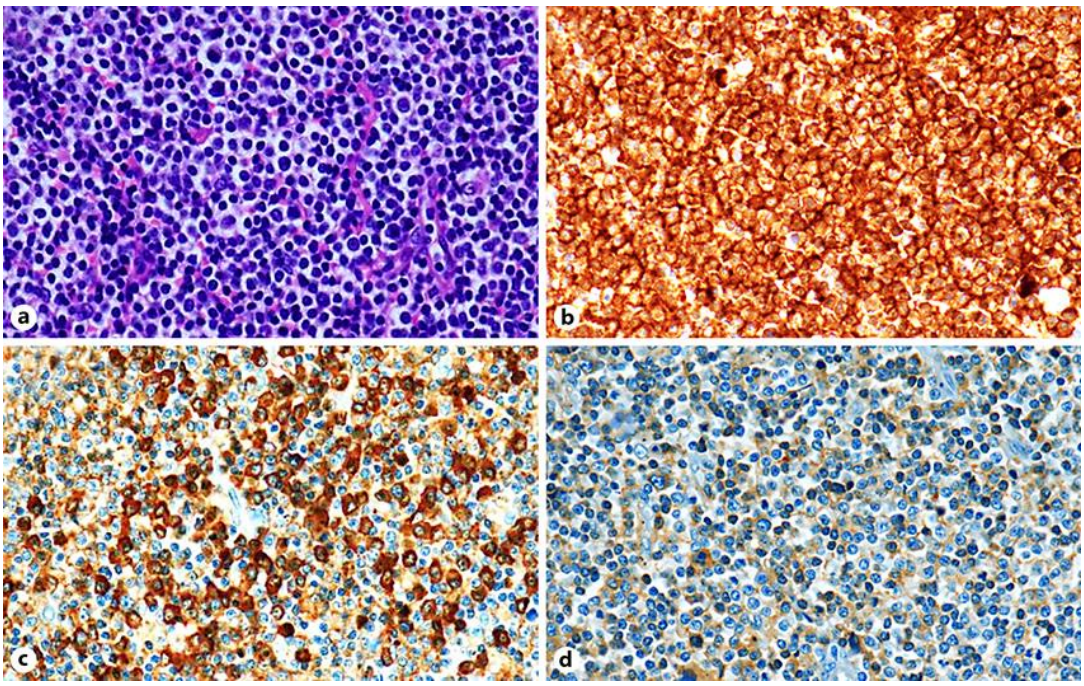

Fig. 2. Pathology and immunohistochemistry of the lymph node. **a** The cells are proliferating monocytoid B cells with pale cytoplasm and round/irregular nuclei. HE. ×400. **b** Immunohistochemically, the cells are positive for CD20. **c**, **d** Immunohistochemical staining for kappa (**c**) and lambda (**d**) showed light chain of plasma cell restriction for kappa.