Development of diffuse large B-cell lymphoma after sofosbuvir-ledipasvir treatment for chronic hepatitis C: A case report and literature review

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Received January 28, 2020; Accepted May 20, 2020

DOI:10.3892/mco.2020.2071

Abstract. Recently, treatments for chronic hepatitis C virus (HCV) infection have significantly improved by the development of direct-acting antiviral agents (DAAs) and almost all patients with HCV can complete antiviral treatment without apparent adverse events. Malignant lymphoma, particularly B-cell non-Hodgkin's lymphoma, is one of the extrahepatic manifestations associated with chronic HCV infection. The effectiveness of anti-HCV therapy with DAAs for B-cell non-Hodgkin's lymphoma has been demonstrated in recent reports, whereas late-onset B-cell non-Hodgkin's lymphoma after HCV eradication with DAAs has occasionally been reported. In the present study, a 77-year-old man with chronic hepatitis C and intermediate liver cancer risk received sofosbuvir-ledipasvir treatment for 12 weeks. Two months following the end of antiviral therapy, he had achieved sustained virologic response for 8 weeks. However, the patient occasionally found swelling of the right cervical lymph nodes without any subjective symptoms. Lymph node biopsy revealed diffuse large B-cell lymphoma and whole-body ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography with computed tomography showed increased FDG uptake in the right cervical, right submandibular, mediastinal and mesenteric lymph nodes. The patient received six courses of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone chemotherapy and achieved complete response at 8 months after chemotherapy initiation. Thus, the development of lymphoid malignancies may arise, even after HCV eradication with DAAs. Therefore, clinicians should be aware of such risks during and after antiviral treatment with DAAs.

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Key words: antiviral therapy, diffuse large B-cell lymphoma, direct-acting antiviral agents, hepatitis C virus, ledipasvir, sofosbuvir

Introduction

A total of >180 million people are chronically infected with hepatitis C virus (HCV) worldwide and chronic HCV infection may lead to the development of chronic hepatitis, liver cirrhosis and hepatocellular carcinoma (HCC) (1). Once patients have progressed to liver cirrhosis, there is an annual 3-5% risk of developing HCC (2). Recently, treatment of HCV infection has been revolutionized by the development of direct-acting antiviral agents (DAAs) and sustained virologic response (SVR) rates of >90% have been achieved, regardless of the HCV genotype (3). In addition, interferon (IFN)-free regimens have enabled patients with HCV who are ineligible for conventional IFN therapy owing to depression, cytopenia, and autoimmune diseases to be cured of HCV infection without any severe adverse events (4).

Lymphoproliferative disorders, including B-cell non-Hodgkin's lymphomas (NHLs), are important extrahepatic manifestations associated with chronic HCV infection (5). The most common B-cell NHLs in HCV-infected patients are marginal zone lymphomas (MZLs), diffuse large B-cell lymphomas (DLBCLs) and lymphoplasmacytic lymphoma (6). The pathogenesis of HCV-related lymphomagenesis is still under investigation; however, chronic antigen stimulation and genetic mutations arising from HCV-induced replication proteins are the most accepted mechanisms (5,7).

IFN-free DAA treatment for HCV is associated with high success rates of viral clearance and significantly improved overall and disease-free survival following curative treatment in patients with HCV-related HCC (8-10). Previous studies reported that anti-HCV treatment with IFN-free DAAs induced clinical remission of HCV-related indolent, low-grade B-cell NHLs (11-18), and concomitant or subsequent use of DAAs with chemotherapy resulted in higher disease-free survival rates in patients with HCV-related DLBCL compared with chemotherapy alone (13,19,20). Thus, anti-HCV treatment with DAAs has been suggested as a possible therapeutic intervention for patients with HCV-related lymphoproliferative disorders, particularly in terms of improving patient outcomes (17,19-21). Although recent studies have reported late-onset B-cell NHLs following HCV clearance with DAAs (22-26) (Table I),

the mechanisms underlying this association have not been clarified. Accordingly, the current study presents a case of a patient with DLBCL occurring after HCV clearance with sofosbuvir-ledipasvir treatment and discusses the possible underlying mechanisms by reviewing recent publications.

Case report

A 61-year-old man was diagnosed with chronic hepatitis C in April 2000 and treated by conventional IFN monotherapy for 24 weeks from August 2000 to January 2001. However, he did not achieve SVR and was subsequently treated with ursodeoxycholic acid (UDCA) at a local clinic. He was followed up every 3 months and serum alanine aminotransferase (ALT) levels remained normal for 15 years. In February 2016, when the patient was 77 years of age, he was admitted to Gifu University Hospital (Gifu, Japan) to evaluate the indication of IFN-free DAA treatment. His HCV was genotyped as 1b with an HCV RNA 6.5 log IU/ml and no genetic alterations were observed in both non-structural protein 3 (NS3) and non-structural protein 5A (NS5A) regions. Imaging studies with systemic dynamic computed tomography showed the appearance of chronic liver damage, as demonstrated by blunting of the liver edge; however, neither liver cirrhosis nor hepatocellular carcinoma were observed. Moreover, no detectable lymph node swelling was observed. Although serum ALT levels and platelet counts were normal, the patient was categorized into the intermediate liver cancer risk group owing to his advanced age. Therefore, according to the treatment guidelines for chronic hepatitis C published by The Japan Society of Hepatology (4), 12 weeks of sofosbuvir-ledipasvir treatment were initiated in March 2016 to reduce the risk of liver cancer in this patient. Serum HCV RNA levels rapidly decreased to an undetectable level at week 4 of treatment and serum ALT levels remained normal without UDCA. Thereafter, sofosbuvir-ledipasvir treatment was completed as scheduled in May 2016 without any adverse events.

In July 2016, 2 months after the end of sofosbuvir-ledipasvir treatment, the patient had occasionally found swelling of the right cervical lymph nodes, although no subjective symptoms such as fever, night sweats and body weight loss were observed. Lymph node biopsy revealed diffuse proliferation of large abnormal cells (Fig. 1A) and immunostaining confirmed the expression of CD20 (Fig. 1B) and CD79α (Fig. 1C) in abnormal cells, leading to a diagnosis of DLBCL. Additionally, the Ki-67 proliferation index of the abnormal cells was ~80% (Fig. 1D). Whole-body ^{18}F-fluorodeoxyglucose positron emission tomography with computed tomography (FDG-PET/CT) showed increased FDG uptake in the right cervical, right submandibular (Fig. 2A), mediastinal (Fig. 2B) and mesenteric (Fig. 2C) lymph nodes and maximum standardized uptake values in these lesions were 18.83, 10.38, 4.75 and 4.89, respectively. In addition, no extranodal sites were observed in the imaging study or bone marrow examinations. Laboratory analyses revealed slight elevation of serum soluble interleukin-2 receptor (sIL-2R); however, no abnormal values were observed in peripheral blood or biochemistry, including lactate dehydrogenase (Table II). Based on the above aforementioned clinical data, his DLBCL was evaluated as follows: Ann Arbor stage IIIA; International Prognostic Index (IPI), low-intermediate. Thereafter, he received six courses of

Table I. Reported cases of late-onset B-cell NHLs after HCV clearance with DAAs.

Author, year	Age (years)/sex	Liver status	Antiviral agents	Time to onset of NHLs after antiviral treatment	Histological classification of NHLs	Gene mutation	Treatment for NHLs	Outcome	(Refs.)
Lin *et al*, 2016	69 M	CH	SOF/RBV	1	Aggressive MCL	N/A	R-hyperCVAD	PR	(22)
Lin *et al*, 2016	61 M	CH	SOF/RBV	1	Aggressive MCL	p53	R-hyperCVAD	SD	(22)
Ohzato *et al*, 2017	81 F	CH	SOF/LDV	7	DLBCL	N/A	Tumor resection	CR	(23)
Rodríguez de Santiago *et al*, 2018	73 M	LC	SOF/LDV/RBV	10	MZL	N/A	R-B	PR	(24)
Rodríguez de Santiago *et al*, 2018	62 F	LC	SOF/LDV	19	Indolent MCL	N/A	No treatment (Follow up)	SD	(24)
Andrade *et al*, 2018	55 M	LC	SOF/RBV	12	DLBCL	N/A	R-CHOP	N/A	(25)
Iwane *et al*, 2019	70 M	CH	SOF/LDV	1	DLBCL	N/A	R-DeVIC	CR	(26)
Current study	77 M	CH	SOF/LDV	2	DLBCL	N/A	R-CHOP	CR	-

CH, chronic hepatitis; CR, complete response; DAAs, direct-acting antiviral agents; DLBCL, diffuse large B-cell lymphoma; HCV, hepatitis C virus; LC, liver cirrhosis; LDV, ledipasvir; MCL, mantle-cell lymphoma; MZL, marginal zone lymphoma; N/A, not applicable; NHLs, non-Hodgkin's lymphomas; No., number; PR, partial response; RBV, ribavirin; R-B, rituximab and bendamustine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, oncovin and prednisolone; R-DeVIC, rituximab, carboplatin, etoposide, ifosfamide and dexamethasone; Refs., References; R-hyperCVAD, rituximab, cyclophosphamide, vincristine, doxorubicin and dexamethasone; SD, stable disease; SOF, sofosbuvir; M, male; F, female.

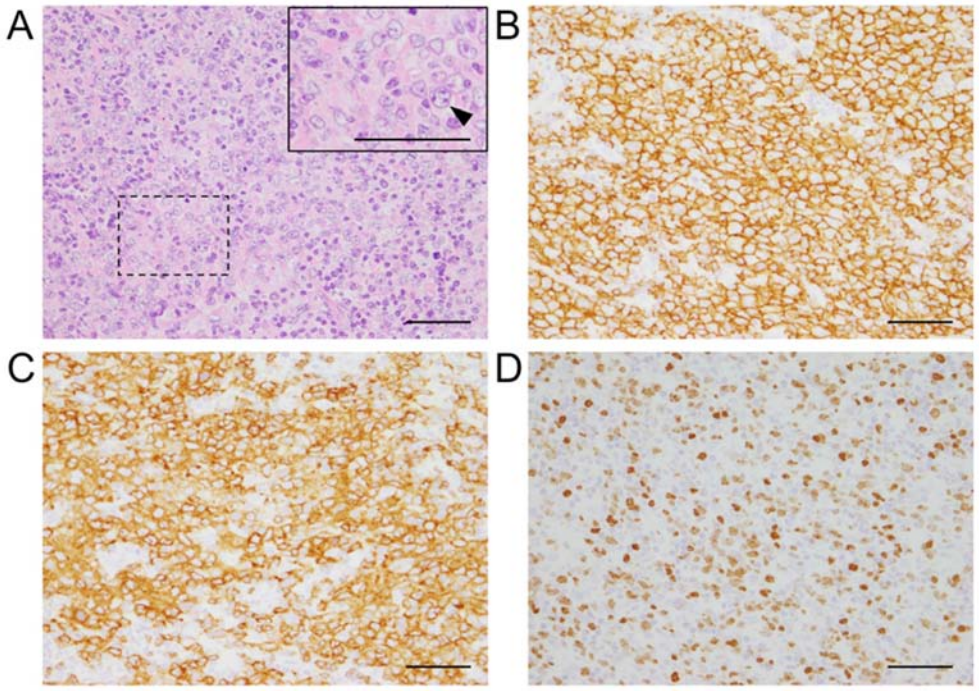

Figure 1. Pathological findings of the biopsied lymph node. (A) Hematoxylin and eosin staining of the biopsy specimen showed diffuse proliferation of large abnormal cells with irregular nuclei. Arrowhead: A representative large abnormal cell containing a relatively large nucleolus. Rectangular area with solid line: Enlarged image of the regions enclosed within the dotted line. Scale bar, 50 μm. Immunohistochemical staining of (B) CD20, (C) CD79α and (D) Ki-67 indicated that abnormal cells were diffusely positive for CD20 and CD79α, and ~80% of those cells were positive for Ki-67. Scale bar, 50 μm.

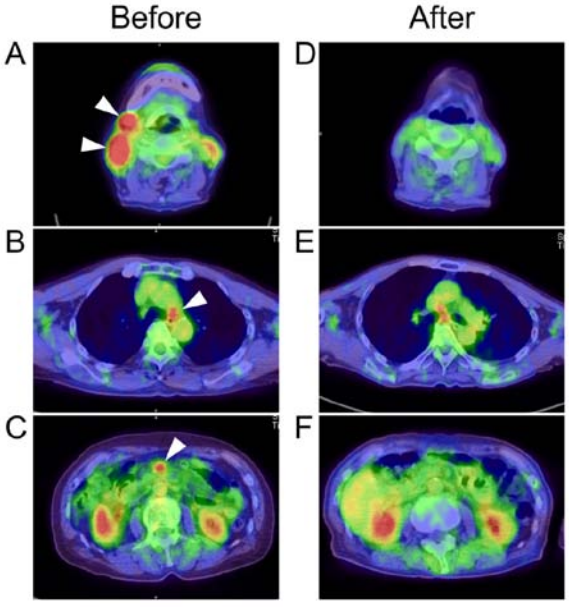

Figure 2. FDG-PET/CT images before and after R-CHOP chemotherapy. (A-C) FDG-PET/CT images before R-CHOP chemotherapy. Arrowheads: Abnormal uptake of FDG in the right cervical (A: lower arrow), right submandibular (A: upper arrow), mediastinal (B) and mesenteric (C) lymph nodes. (D-F) FDG-PET/CT images after R-CHOP chemotherapy. Abnormal FDG uptake observed before R-CHOP chemotherapy disappeared after treatment. FDG-PET/CT, ^{18}F-fluorodeoxyglucose positron emission tomography with computed tomography; R-CHOP, rituximab, cyclophosphamide, doxorubicin, oncovin and prednisolone.

R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone) chemotherapy between September 2016 to December 2016 and achieved complete response for DLBCL in February 2017, as shown by FDG-PET/CT after R-CHOP treatment (Fig. 2D-F). No recurrence of HCV RNA or DLBCL was observed for at least 3 years after chemotherapy.

Histological examination was performed on biopsied lymph node specimens fixed with 10% formalin for 24 h at room temperature. Paraffin-embedded tissues were cut into 4 μm-thick sections and deparaffinized. These sections were stained with hematoxylin and eosin or used for immunohistochemical analysis. For hematoxylin and eosin staining, the sections were stained with 0.1% hematoxylin solution for 4 min at room temperature and then stained with 0.1% eosin Y (cat. no. 058-00062; Wako Pure Chemical Industries, Ltd.) solution for 2 min at room temperature. For immunohistochemistry, the deparaffinized sections were placed in a citrate buffer solution (pH 6.0), and then autoclaved at 121˚C for 1 min for antigen retrieval. The sections were then rinsed and blocked with 3% hydrogen peroxide in methanol for 10 min to remove endogenous peroxidase activity. Non-specific binding sites were blocked in 0.01 M phosphate-buffered saline containing 2% bovine serum albumin (cat. no. 019-07494; Wako Pure Chemical Industries, Ltd.) for 30 min. The sections were then incubated overnight at 4˚C with the following antibodies in blocking buffer: Anti-CD20 [1:200, mouse immunoglobulin G (IgG); cat. no. NCL-L-CD20-L26; Leica Biosystems Inc.], anti-CD79α (1:200, mouse IgG; cat. no. IR621; Dako; Agilent Technologies, Inc.), and anti-Ki-67 (1:200; mouse IgG, cat. no. M7240; Dako; Agilent Technologies, Inc.). These antibodies were detected using a biotinylated anti-mouse IgG (1:300; cat. no. E0433; Dako; Agilent Technologies, Inc.) for 30 min at room temperature, followed by incubation with avidin-coupled peroxidase (Vectastain ABC kit; Vector Laboratories, Inc.; Maravai LifeSciences) for 30 min at room

Table II. Laboratory data at the time of DLBCL diagnosis.

Parameter	Data	N.R.
WBC (cells/μl)	5,270	3,300-8,600
RBC (x10^6/μl)	5.32	4.35-5.55
Hb (g/dl)	14.5	13.7-16.8
Ht (%)	44	40.7-50.1
Plt (x10^3/μl)	167	158-348
TP (g/dl)	7.4	6.6-8.1
Alb (g/dl)	4.4	4.1-5.1
AST (U/l)	19	15-30
ALT (U/l)	11	10-42
LDH (U/l)	201	124-222
ALP (U/l)	286	106-322
γ-GTP (U/l)	13	13-64
T.Bil (mg/dl)	0.7	0.4-1.5
UN (mg/dl)	19.3	8.0-20.0
Cr (mg/dl)	0.88	0.65-1.07
Na (mmol/l)	140	134-145
K (mmol/l)	4.2	3.6-4.8
Cl (mmol/l)	107	101-108
CRP (mg/dl)	0.07	<0.14
FBS (mg/dl)	94	73-109
HbA1c (%)	5.4	4.9-6.0
PT (%)	100	70-130
FIB (mg/dl)	357	200-400
FDP (μg/ml)	2.5	<5.0
D-dimer (μg/ml)	1.5[a]	<1.0
IgG (mg/dl)	1363	861-1,747
IgA (mg/dl)	266	93-393
IgM (mg/dl)	71	33-183
β2-MG (mg/l)	2.3[a]	1.0-1.9
sIL-2R (U/ml)	899[a]	122-496
HCV-Ab	(+)	(-)
HCV-RNA (Log IU/ml)	N.D.	N.D.
HBs-Ag	(-)	(-)
HBs-Ab	(-)	(-)
HBc-Ab	(-)	(-)
HIV-1/2 Ab	(-)	(-)
HTLV-1 Ab	(-)	(-)
AFP (ng/ml)	2.3	<10

[a]Increased compared with normal range. AFP, alpha-fetoprotein; Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; β2-MG, beta 2-microglobulin; Cl, chloride; Cr, creatinine; CRP, C-reactive protein; DLBCL, diffuse large B-cell lymphoma; FBS, fasting blood glucose; FDP, fibrin degradation product; FIB, fibrinogen; γ-GTP, gamma-glutamyl transpeptidase; Hb, hemoglobin; HbA1c, hemoglobin A1c; HBc-Ab, hepatitis B virus core antibody; HBs-Ab, hepatitis virus B surface antibody; HBs-Ag, hepatitis virus B surface antigen; HCV-Ab, hepatitis C virus antibody; HIV, human immunodeficiency virus; Ht, hematocrit; HTLV-1, human T-cell leukemia virus type 1; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; K, potassium; LDH, lactate dehydrogenase; Na, sodium; N.D., no detection; N.R., normal range; Plt, platelet; PT, prothrombin; RBC, red blood cell; sIL-2R, soluble interleukin-2 receptor; T.Bil, total bilirubin; TP, total protein; UN, urea nitrogen; WBC, white blood cell.

temperature. The peroxidase binding sites were visualized by incubation with 3,3'-diaminobenzidine in 50 mM Tris-EDTA buffer and counterstained with hematoxylin for a few seconds at room temperature. These sections were then observed using a light microscope (magnification, x400; Olympus BX53; Olympus Corporation).

Discussion

The present case report presented a case of a patient with DLBCL occurring early after HCV clearance with sofosbuvir-ledipasvir treatment. Previous publications reported that HCV clearance with DAAs improved outcomes in patients with HCV-related B-cell NHLs (11-20), whereas late-onset B-cell NHLs after HCV clearance with DAAs have occasionally been reported (22-26). Thus far, only seven cases have been reported since 2016 (22-26) (Table I) and the underlying mechanisms remain to be elucidated.

Lymphoproliferative disorders are important extrahepatic manifestations associated with chronic HCV infection (6). A recent meta-analysis of epidemiological studies showed that HCV-seropositive patients have an estimated 5- to 10-fold increased risk for B-cell NHLs compared with the general population (27,28). Thus, patients with chronic HCV infection are at higher risk of B-cell NHLs.

Currently, the pathogenesis of HCV-related lymphomagenesis remains unclear. However, the following three general theories have been proposed to explain the association (5). First, B-cell receptors are continuously stimulated by external HCV viral antigens, leading to consecutive B-cell proliferation. Second, HCV replication inside B-cells produces HCV-derived viral proteins that induce genetic damage in the B-cells. Third, permanent genetic B-cell damage can be caused by transient intracellular HCV infection. Indeed, several basic studies have shown that the HCV envelope protein E3 binds to CD81, a surface protein on B-lymphocytes, and forms a costimulatory complex with CD19 and CD21, which in turn stimulates intracellular proliferative signals (29,30). Moreover, acute or chronic HCV infections are known to be associated with increased frequencies of *BCL-6* and *p53* gene mutations in B-cells *in vitro*; mutations in these genes have been linked to DLBCL (31). Accordingly, HCV-related lymphomagenesis may be attributed to either chronic viral antigen stimulation or genetic mutations that lead to the clonal expansion and malignant transformation of B-cells, as previously reported (7,5,25).

During the past few years, several clinical studies have evaluated extrahepatic malignancies after DAA treatment for chronic HCV infection. A retrospective cohort study showed that three of 431 patients who received DAA treatment were diagnosed with DLBCL after HCV eradication; the prevalence in this cohort was 696 per 100,000, which was ~30 times higher compared with the general population (32). In addition, El-Serag *et al* (1) also reported that successful DAA treatment resulting in SVR was not associated with reduction in NHL risk. Moreover, in a comparative study of the risk of hematologic malignancies following IFN-induced SVR and DAA-induced SVR, researchers showed that IFN-induced SVR significantly reduced the risk of hematologic malignancies, including lymphoma and myeloma (adjusted hazard ratio, 0.67; 95% confidence interval, 0.53-0.84), whereas

DAA-induced SVR was not associated with a reduction in the risk of hematologic malignancies (adjusted hazard ratio, 1.08; 95% confidence interval, 0.66-1.78) (33). Thus, these results suggested that the development of malignant lymphomas may occur after HCV clearance with DAAs, supporting recent case reports (22-26), including the present case (Table I).

As shown in Table I, only seven cases of late-onset B-cell NHLs after HCV clearance with DAAs have been reported since 2016 (22-26). Currently, the underlying mechanisms remain unclear. However, several possible mechanisms have been proposed in recent publications. Andrade *et al* (25) suggested that HCV-induced genetic damage produced a survival signal in B-cells, which may lead to late transformation, even years after successful HCV therapy. Indeed, genetic mutations derived from either acute or chronic HCV infection are known to persist, even after HCV clearance (31). Notably, unlike conventional IFN therapy, DAAs lack the ability to either directly treat a subclinical malignancy or enhance an immune response to malignancy (33). In particular, in terms of immune response, HCV clearance with DAAs was reported to be associated with the persistence of CD4 regulatory T cells (34), which inhibit cytotoxic $CD8^+$ T cells exposed to B-cell NHLs (35). Moreover, Reig *et al* (36) suggested that DAA-induced SVR promotes a hyporesponsive state of memory helper T cells to tumor antigen, which may leave patients who overcame HCV infection vulnerable to the development of malignancies. Thus, it is plausible that premalignant B-cells with genetic mutations may survive by escaping immune surveillance after HCV clearance with DAAs, leading to transformation of these B-cells into malignant clones, such as DLBCL.

Although it is still unclear whether DAAs have direct effects on tumor development, a previous clinical study revealed an association between DAA treatment and serum vascular endothelial growth factor (VEGF) levels (37). The levels of serum VEGF during DAA treatment in patients with HCV were approximately 4-fold higher than those during pretreatment, and serum VEGF levels remained elevated through the end of treatment (37). Notably, increased VEGF expression is also observed in serum or tissues in hematologic malignancies, thereby accelerating tumor growth by promoting angiogenesis and vasopermeability (38). In particular, DLBCL frequently expresses VEGF and its receptors VEGFR-1 and VEGFR-2, both of which are correlated with the development of DLBCL via autocrine and paracrine mechanisms (39). Based on these findings, extrinsic VEGF induced by DAA treatment may also be associated with the development of DLBCL.

In all cases presented in Table I, the patients were treated with antiviral regimens, including sofosbuvir, a new class of specific nucleotide analog inhibitors of HCV NS5B polymerase (22). To date, sofosbuvir has been reported to be effective in treating HCV-related MZL (17,18); however, to the best of our knowledge, this agent has not been reported to induce lymphomagenesis as an adverse effect. Further studies are needed to investigate whether sofosbuvir indeed induces lymphomagenesis. In addition, one case presented in Table I included a p53 gene mutation in the NHL of the patient (22); however, any common genetic mutations in the previously reported cases and the current case are unknown due to the lack of information available from the previous reports (22-26). Currently, to the best of our knowledge, there are no reports demonstrating an association between p53 gene mutation in B-cells and sofosbuvir treatment.

Several possible mechanisms of late-onset B-cell NHL after successful DAA treatment have been reported in the recent publications described above; however, the detailed mechanisms remain unclear owing to the small number of reported cases and the small sample size in each study. More clinical studies are needed to elucidate the relationships between DAA treatment and late-onset B-cell NHLs after successful antiviral therapy.

In conclusion, the present study reported the case of a patient with DLBCL that occurred early after HCV clearance with sofosbuvir-ledipasvir treatment. The development of lymphoid malignancies may occur, even after successful HCV treatment with DAAs. Therefore, clinicians should be aware of such risks during and after antiviral treatment with DAAs.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

Authors' contributions

HS and MShim collaborated in the conception and design of the study. HS, TM, YI, TH, NN, KI, JK and YS performed the case study and acquired the data and images for the case. HS performed data analysis and interpretation and wrote the manuscript. HS, KI, NK, AS, KT, MShir, and MShim revised the manuscript and MShim supervised manuscript preparation. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was provided by the patient for publication of this study.

Competing interests

The authors declare that they have no competing interests.

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