

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 ¹⁸F-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.

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),

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

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 urso-deoxycholic 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 CD79 α (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 ¹⁸F-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 <i>et al</i> , 2016	69 M	CH	SOF/RBV	1	Aggressive MCL	N/A	R-hyperCVAD	PR (22)
Lin <i>et al</i> , 2016	61 M	CH	SOF/RBV	1	Aggressive MCL	p53	R-hyperCVAD	SD (22)
Ohzato <i>et al</i> , 2017	81 F	CH	SOF/LDV	7	DLBCL	N/A	Tumor resection	CR (23)
Rodríguez de Santiago <i>et al</i> , 2018	73 M	LC	SOF/LDV/RBV	10	MZL	N/A	R-B	PR (24)
Rodríguez de Santiago <i>et al</i> , 2018	62 F	LC	SOF/LDV	19	Indolent MCL	N/A	No treatment (Follow up)	SD (24)
Andrade <i>et al</i> , 2018	55 M	LC	SOF/RBV	12	DLBCL	N/A	R-CHOP	N/A (25)
Iwane <i>et al</i> , 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 dexmethasone; Refs., References; R-hyperCVAD, rituximab, cyclophosphamide, vincristine, doxorubicin and dexmethasone; SD, stable disease; SOF, sofosbuvir; M, male; F, female.

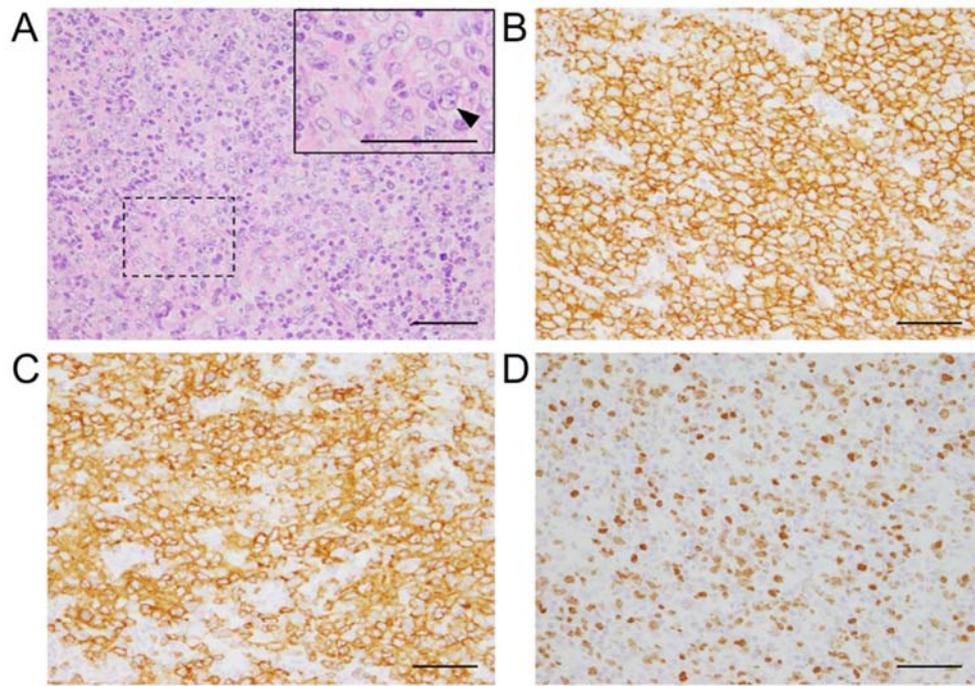


Figure 1. Pathological findings of the biopsied lymph node. (A) Hematoxylin and eosin staining of the biopsy specimen showed diffuse proliferation of large abnormal cells with irregular nuclei. Arrowhead: A representative large abnormal cell containing a relatively large nucleolus. Rectangular area with solid line: Enlarged image of the regions enclosed within the dotted line. Scale bar, 50 μ m. Immunohistochemical staining of (B) CD20, (C) CD79 α and (D) Ki-67 indicated that abnormal cells were diffusely positive for CD20 and CD79 α , and ~80% of those cells were positive for Ki-67. Scale bar, 50 μ m.

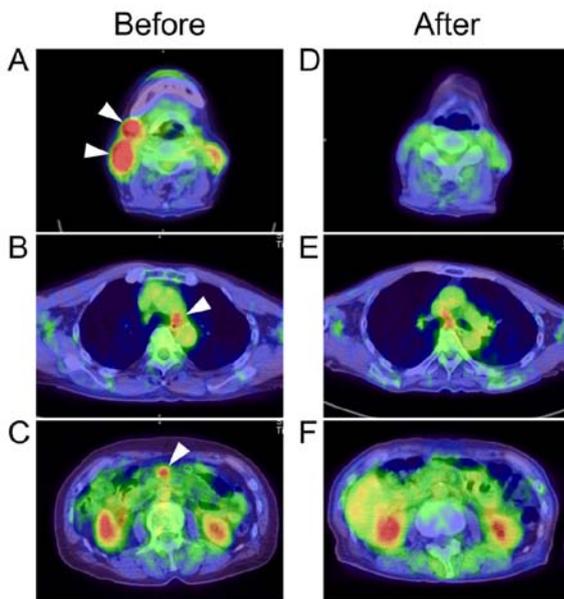


Figure 2. FDG-PET/CT images before and after R-CHOP chemotherapy. (A-C) FDG-PET/CT images before R-CHOP chemotherapy. Arrowheads: Abnormal uptake of FDG in the right cervical (A: lower arrow), right submandibular (A: upper arrow), mediastinal (B) and mesenteric (C) lymph nodes. (D-F) FDG-PET/CT images 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 μ m-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-CD79 α (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/ μ l)	5,270	3,300-8,600
RBC ($\times 10^6/\mu$ l)	5.32	4.35-5.55
Hb (g/dl)	14.5	13.7-16.8
Ht (%)	44	40.7-50.1
Plt ($\times 10^3/\mu$ l)	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 (μ g/ml)	2.5	<5.0
D-dimer (μ g/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
β 2-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

^aIncreased compared with normal range. AFP, alpha-fetoprotein; Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; β 2-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, $\times 400$; 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.

References

1. El-Serag HB, Christie IC, Puenpatom A, Castillo D, Kanwal F and Kramer JR: The effects of sustained virological response to direct-acting anti-viral therapy on the risk of extrahepatic manifestations of hepatitis C infection. *Aliment Pharmacol Ther* 49: 1442-1447, 2019.
2. Fattovich G, Stroffolini T, Zagni I and Donato F: Hepatocellular carcinoma in cirrhosis: Incidence and risk factors. *Gastroenterology* 127 (5 Suppl 1): S35-S50, 2004.

3. Pawlotsky JM, Feld JJ, Zeuzem S and Hoofnagle JH: From non-A, non-B hepatitis to hepatitis C virus cure. *J Hepatol* 62 (Suppl 1): S87-S99, 2015.
4. Drafting Committee for Hepatitis Management Guidelines, the Japan Society of Hepatology. JSH Guidelines for the management of hepatitis C virus infection: A 2014 update for genotype 1. *Hepatol Res* 44 (Suppl S1): S59-S70, 2014.
5. Peveling-Oberhag J, Arcaini L, Hansmann ML and Zeuzem S: Hepatitis C-associated B-cell non-Hodgkin lymphomas. Epidemiology, molecular signature and clinical management. *J Hepatol* 59: 169-177, 2013.
6. de Sanjose S, Benavente Y, Vajdic CM, Engels EA, Morton LM, Bracci PM, Spinelli JJ, Zheng T, Zhang Y, Franceschi S, *et al*: Hepatitis C and non-Hodgkin lymphoma among 4784 cases and 6269 controls from the International Lymphoma Epidemiology Consortium. *Clin Gastroenterol Hepatol* 6: 451-458, 2008.
7. Carloni G, Fioretti D, Rinaldi M and Ponzetto A: Heterogeneity and coexistence of oncogenic mechanisms involved in HCV-associated B-cell lymphomas. *Crit Rev Oncol Hematol* 138: 156-171, 2019.
8. Dang H, Yeo YH, Yasuda S, Huang CF, Iio E, Landis C, Jun DW, Enomoto M, Ogawa E, Tsai PC, *et al*: Cure with interferon free DAA is associated with increased survival in patients with HCV related HCC from both East and West. *Hepatology* 71: 1910-1922, 2019.
9. Ikeda K, Kawamura Y, Kobayashi M, Kominami Y, Fujiyama S, Sezaki H, Hosaka T, Akuta N, Saitoh S, Suzuki F, *et al*: Direct-acting antivirals decreased tumor recurrence after initial treatment of hepatitis C virus-related hepatocellular carcinoma. *Dig Dis Sci* 62: 2932-2942, 2017.
10. Imai K, Takai K, Hanai T, Suetsugu A, Shiraki M and Shimizu M: Sustained virological response by direct-acting antivirals reduces the recurrence risk of hepatitis C-related hepatocellular carcinoma after curative treatment. *Mol Clin Oncol* 12: 111-116, 2020.
11. Michot JM, Canioni D, Driss H, Alric L, Cacoub P, Suarez F, Sibon D, Thieblemont C, Dupuis J, Terrier B, *et al*: Antiviral therapy is associated with a better survival in patients with hepatitis C virus and B-cell non-Hodgkin lymphomas, ANRS HC-13 lympho-C study. *Am J Hematol* 90: 197-203, 2015.
12. Arcaini L, Besson C, Frigeni M, Fontaine H, Goldaniga M, Casato M, Visentini M, Torres HA, Loustaud-Ratti V, Peveling-Oberhag J, *et al*: Interferon-free antiviral treatment in B-cell lymphoproliferative disorders associated with hepatitis C virus infection. *Blood* 128: 2527-2532, 2016.
13. Nicolini LA, Zappulo E, Viscoli C and Mikulska M: Management of chronic viral hepatitis in the hematological patient. *Expert Rev Anti Infect Ther* 16: 227-241, 2018.
14. Rossotti R, Travi G, Pazzi A, Baiguera C, Morra E and Puoti M: Rapid clearance of HCV-related splenic marginal zone lymphoma under an interferon-free, NS3/NS4A inhibitor-based treatment. A case report. *J Hepatol* 62: 234-237, 2015.
15. Merli M, Carli G, Arcaini L and Visco C: Antiviral therapy of hepatitis C as curative treatment of indolent B-cell lymphoma. *World J Gastroenterol* 22: 8447-8458, 2016.
16. Arcaini L, Rossi D and Paulli M: Splenic marginal zone lymphoma: From genetics to management. *Blood* 127: 2072-2081, 2016.
17. Hirose S, Yamaji Y, Tsuruya K, Ogawa Y, Miyaoka M and Kagawa T: Rapid regression of B-cell non-Hodgkin's lymphoma after eradication of hepatitis C virus by direct antiviral agents. *Case Rep Gastroenterol* 13: 336-341, 2019.
18. Carrier P, Jaccard A, Jacques J, Tabouret T, Debette-Gratien M, Abraham J, Mesturoux L, Marquet P, Alain S, Sautereau D, *et al*: HCV-associated B-cell non-Hodgkin lymphomas and new direct antiviral agents. *Liver Int* 35: 2222-2227, 2015.
19. Persico M, Aglitti A, Caruso R, De Renzo A, Selleri C, Califano C, Abenavoli L, Federico A and Masarone M: Efficacy and safety of new direct antiviral agents in hepatitis C virus-infected patients with diffuse large B-cell non-Hodgkin's lymphoma. *Hepatology* 67: 48-55, 2018.
20. Merli M, Frigeni M, Gotti M, Grossi P, Bruno R, Passamonti F and Arcaini L: Direct-acting antivirals during or after immunochemotherapy in hepatitis C virus-positive diffuse large B-cell lymphomas. *Hepatology* 66: 1341-1343, 2017.
21. Zignego AL, Ramos-Casals M, Ferri C, Saadoun D, Arcaini L, Roccatello D, Antonelli A, Desbois AC, Comarmond C, Gragnani L, *et al*: International therapeutic guidelines for patients with HCV-related extrahepatic disorders. A multidisciplinary expert statement. *Autoimmun Rev* 16: 523-541, 2017.
22. Lin RJ, Moskovits T, Dieffenbach CS and Hymes KB: Development of highly aggressive mantle cell lymphoma after sofosbuvir treatment of hepatitis C. *Blood Cancer J* 6: e402, 2016.
23. Ohzato Y, Murakami M, Shimizu J, Koga C, Marukawa D, Yoshida Y, Yasuyama A, Matsumura T, Takada A, Kameda C, *et al*: A case report of inguinal malignant lymphoma after surgery for hepatocellular carcinoma. *Gan To Kagaku Ryoho* 44: 1638-1640, 2017 (In Japanese).
24. Rodríguez de Santiago E, Velázquez Kennedy K, García González M, Gea Rodríguez F, Téllez Villajos L, Tavío Hernández E and Albillos A: HCV-positive lymphoma after sustained virological response with direct-acting antiviral agents: The game is not over after HCV eradication. *J Viral Hepat* 25: 614-615, 2018.
25. Andrade XA, Paz LH, Nassar M, Oramas DM, Fuentes HE, Kovarik P, Mishra S and Singh A: Primary liver diffuse large B-cell lymphoma following complete response for hepatitis C infection after direct antiviral therapy. *Acta Haematol* 139: 77-80, 2018.
26. Iwane K, Kayahara T, Takabatake H, Morimoto Y, Iseki A, Mizuno M and Notohara K: Recurrence of malignant lymphoma immediately after treatment for hepatitis C virus using direct-acting antivirals. *Nihon Shokakibyō Gakkai Zasshi* 116: 177-183, 2019 (In Japanese).
27. Gisbert JP, García-Buey L, Pajares JM and Moreno-Otero R: Prevalence of hepatitis C virus infection in B-cell non-Hodgkin's lymphoma: Systematic review and meta-analysis. *Gastroenterology* 125: 1723-1732, 2003.
28. Matsuo K, Kusano A, Sugumar A, Nakamura S, Tajima K and Mueller NE: Effect of hepatitis C virus infection on the risk of non-Hodgkin's lymphoma: A meta-analysis of epidemiological studies. *Cancer Sci* 95: 745-752, 2004.
29. Rosa D, Saletti G, De Gregorio E, Zorat F, Comar C, D'Oro U, Nuti S, Houghton M, Barnaba V, Pozzato G and Abrignani S: Activation of naive B lymphocytes via CD81, a pathogenetic mechanism for hepatitis C virus-associated B lymphocyte disorders. *Proc Natl Acad Sci USA* 102: 18544-18549, 2005.
30. Carter RH and Fearon DT: CD19: Lowering the threshold for antigen receptor stimulation of B lymphocytes. *Science* 256: 105-107, 1992.
31. Machida K, Cheng KT, Sung VM, Shimodaira S, Lindsay KL, Levine AM, Lai MY and Lai MM: Hepatitis C virus induces a mutator phenotype: Enhanced mutations of immunoglobulin and protooncogenes. *Proc Natl Acad Sci USA* 101: 4262-4267, 2004.
32. Khoury J, Nassar G, Kramsky R and Saadi T: Extrahepatic malignancies after treatment with direct antiviral agents for chronic HCV infection. *J Gastrointest Cancer* 51: 584-590, 2019.
33. Ioannou GN, Green PK, Berry K and Graf SA: Eradication of hepatitis C virus is associated with reduction in hematologic malignancies: Major differences between interferon and direct-acting antivirals. *Hepatology Commun* 3: 1124-1136, 2019.
34. Langhans B, Nischalke HD, Krämer B, Hausen A, Dold L, van Heteren P, Hüneburg R, Nattermann J, Strassburg CP and Spengler U: Increased peripheral CD4⁺ regulatory T cells persist after successful direct-acting antiviral treatment of chronic hepatitis C. *J Hepatol* 66: 888-896, 2017 (In Albanian, English).
35. Yang ZZ, Novak AJ, Ziesmer SC, Witzig TE and Ansell SM: Attenuation of CD8(+) T-cell function by CD4(+)CD25(+) regulatory T cells in B-cell non-Hodgkin's lymphoma. *Cancer Res* 66: 10145-10152, 2006.
36. Reig M, Boix L, Mariño Z, Torres F, Forns X and Bruix J: Liver cancer emergence associated with antiviral treatment: An immune surveillance failure? *Semin Liver Dis* 37: 109-118, 2017.
37. Villani R, Facciorusso A, Bellanti F, Tamborra R, Piscazzi A, Landriscina M, Vendemiale G and Serviddio G: DAAs rapidly reduce inflammation but increase serum VEGF level: A rationale for tumor risk during anti-HCV treatment. *PLoS One* 11: e0167934, 2016.
38. Podar K and Anderson KC: The pathophysiologic role of VEGF in hematologic malignancies: Therapeutic implications. *Blood* 105: 1383-1395, 2005.
39. Gratzinger D, Zhao S, Marinelli RJ, Kapp AV, Tibshirani RJ, Hammer AS, Hamilton-Dutoit S and Natkunam Y: Microvessel density and expression of vascular endothelial growth factor and its receptors in diffuse large B-cell lymphoma subtypes. *Am J Pathol* 170: 1362-1369, 2007.

