ISSN 1948-5182 (online)

World Journal of *Hepatology*

World J Hepatol 2024 February 27; 16(2): 112-299

Published by Baishideng Publishing Group Inc

World Journal of Hepatology

Contents

Monthly Volume 16 Number 2 February 27, 2024

EDITORIAL

REVIEW

MINIREVIEWS

World Journal of Hepatology

Monthly Volume 16 Number 2 February 27, 2024

Contents

World Journal of Hepatology

Monthly Volume 16 Number 2 February 27, 2024

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Hepatology*, Nobuyuki Takemura, MD, PhD, FACS, Professor, Department of Hepato-Biliary-Pancreatic Surgery and Pediatric Surgery, Saitama Medical Center, Saitama Medical University, Saitama 350-8550, Japan. takemuranobu-tky@umin.ac.jp

AIMS AND SCOPE

The primary aim of *World Journal of Hepatology* (*WJH*, *World J Hepatol*) is to provide scholars and readers from various fields of hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJH mainly publishes articles reporting research results and findings obtained in the field of hepatology and covering a wide range of topics including chronic cholestatic liver diseases, cirrhosis and its complications, clinical alcoholic liver disease, drug induced liver disease autoimmune, fatty liver disease, genetic and pediatric liver diseases, hepatocellular carcinoma, hepatic stellate cells and fibrosis, liver immunology, liver regeneration, hepatic surgery, liver transplantation, biliary tract pathophysiology, non-invasive markers of liver fibrosis, viral hepatitis.

INDEXING/ABSTRACTING

The *WJH* is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (ESCI), Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 Edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJH* as 2.4.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Hepatology

ISSN
ISSN 1948-5182 (online)

LAUNCH DATE
October 31, 2009

FREQUENCY
Monthly

PUBLICATION DATE
February 27, 2024

PUBLISHING PARTNER
Department of Infectious Diseases, the Second Affiliated Hospital of Xi'an Jiaotong University

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

Shuang-Suo Dang

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

PUBLISHING PARTNER's OFFICIAL WEBSITE
http://2yuan.xjtu.edu.cn/Html/Departments/Main/Index_21148.html

World Journal of Hepatology

Submit a Manuscript: https://www.f6publishing.com

World J Hepatol 2024 February 27; 16(2): 286-293

DOI: 10.4254/wjh.v16.i2.286

ISSN 1948-5182 (online)

CASE REPORT

Autoimmune hepatitis and primary sclerosing cholangitis after direct-acting antiviral treatment for hepatitis C virus: A case report

Yoshiki Morihisa, Hobyung Chung, Shuichiro Towatari, Daisuke Yamashita, Tetsuro Inokuma

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Mahmoud MZ, Saudi Arabia

Received: November 30, 2023
Peer-review started: November 30, 2023
First decision: December 8, 2023
Revised: December 22, 2023
Accepted: January 16, 2024
Article in press: January 16, 2024
Published online: February 27, 2024

Yoshiki Morihisa, Hobyung Chung, Shuichiro Towatari, Tetsuro Inokuma, Department of Gastroenterology and Hepatology, Kobe City Medical Center General Hospital, Kobe 650-0047, Hyogo, Japan

Daisuke Yamashita, Department of Pathology, Kobe City Medical Center General Hospital, Kobe 650-0047, Hyogo, Japan

Corresponding author: Hobyung Chung, MD, PhD, Doctor, Department of Gastroenterology and Hepatology, Kobe City Medical Center General Hospital, 2-1-1 Minatojimaminami-machi, Chuo-ku, Kobe 650-0047, Hyogo, Japan. teihiroshi@gmail.com

Abstract

BACKGROUND

Chronic hepatitis C virus (HCV) infection is a major global health concern that leads to liver fibrosis, cirrhosis, and cancer. Regimens containing direct-acting antivirals (DAAs) have become the mainstay of HCV treatment, achieving a high sustained virological response (SVR) with minimal adverse events.

CASE SUMMARY

A 74-year-old woman with chronic HCV infection was treated with the DAAs ledipasvir, and sofosbuvir for 12 wk and achieved SVR. Twenty-four weeks after treatment completion, the liver enzyme and serum IgG levels increased, and antinuclear antibody became positive without HCV viremia, suggesting the development of autoimmune hepatitis (AIH). After liver biopsy indicated AIH, a definite AIH diagnosis was made and prednisolone was initiated. The treatment was effective, and the liver enzyme and serum IgG levels normalized. However, multiple strictures of the intrahepatic and extrahepatic bile ducts with dilatation of the peripheral bile ducts appeared on magnetic resonance cholangiopancreatography after 3 years of achieving SVR, which were consistent with primary sclerosing cholangitis.

CONCLUSION

The potential risk of developing autoimmune liver diseases after DAA treatment should be considered.

Key Words: Liver; Hepatitis C virus; Autoimmune hepatitis; Primary sclerosing cholangitis; Immune system; Case report

Core Tip: Direct-acting antivirals (DAAs) for chronic hepatitis C virus (HCV) infection are widely used as a safe and effective treatment intervention. Chronic HCV infection alters the innate and adaptive immune responses, both functionally and phenotypically. Rapid viral clearance following DAAs treatment restores adaptive immune function. Herein, we report a rare case of autoimmune hepatitis and primary sclerosing cholangitis that developed after DAAs treatment for HCV. The potential risk of developing autoimmune liver diseases after DAAs treatment owing to the restoration of host immunity following rapid viral clearance should be considered.

Citation: Morihisa Y, Chung H, Towatari S, Yamashita D, Inokuma T. Autoimmune hepatitis and primary sclerosing cholangitis after direct-acting antiviral treatment for hepatitis C virus: A case report. *World J Hepatol* 2024; 16(2): 286-293
URL: https://www.wjgnet.com/1948-5182/full/v16/i2/286.htm
DOI: https://dx.doi.org/10.4254/wjh.v16.i2.286

INTRODUCTION

Hepatitis C virus (HCV) infection is a growing international concern because of its substantial morbidity and mortality. HCV has a worldwide prevalence of 0.7%, infecting over 56.8 million people, with approximately 1.5 million new infections every year[1]. Most patients (50%-90%) develop chronic infections and chronic liver diseases, such as cirrhosis, liver failure, and hepatocellular carcinoma[2]. Pegylated interferon alpha and ribavirin administration was the basis of the antiviral therapy for HCV; however, the frequent side effects and poor treatment outcomes were problematic[3-5]. In 2013, the first interferon-free treatment regimen was approved for the treatment of chronic hepatitis C (CHC) and several other direct-acting antivirals (DAAs) have been developed since. Such DAA regimens present excellent safety profiles and high response rates, which exceed 97% not only in clinical trials, but also in real-world clinical settings. As a result, most patients with CHC have achieved sustained virological response (SVR)[6,7].

Recently, various studies have focused on the functional changes of the immune system induced by the rapid viral clearance of DAAs after chronic HCV infections, and some reports have demonstrated the recovery of innate and adaptive immune responses after the SVR[8]. Interestingly, some case reports have described patients who developed autoimmune hepatitis (AIH) after DAA treatment for HCV, suggesting that the recovery of host immunity is associated with the development of autoimmune liver disorders.

Herein, we report a rare case of a woman with CHC who developed AIH and primary sclerosing cholangitis (PSC) after antiviral therapy with DAA.

CASE PRESENTATION

Chief complaints

A 74-year-old woman visited our department for the treatment of HCV infection.

History of present illness

She was administered a 12-wk combination regimen of sofosbuvir (SOF) and ledipasvir (LDV) and achieved SVR. Twenty-four weeks after treatment completion, the liver enzyme levels increased.

History of past illness

She had a history of ectopic pregnancy and had received a blood transfusion 50 years before.

Personal and family history

She had no remarkable family history or history of autoimmune diseases. She had a history of smoking and consumed 350 mL of beer once a week.

Physical examination

She denied having fever or chills, malaise, or fatigue but presented discrete weight loss.

Laboratory examinations

Laboratory examinations showed an undetectable serum HCV RNA; however, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were elevated at 335 U/L and 329 U/L, respectively (Table 1). The total bilirubin level was not increased, and prothrombin time was not prolonged. The serum IgG level was increased at 3481 mg/dL. The antinuclear antibody (ANA) and antismooth muscle antibody (ASMA) titers were 1:80 in a homogeneous

Table 1 Blood test

Blood test	Value	Unit
Hematology		
WBC	59.00	$\times 10^2/\mu L$
RBC	400.00	$\times 10^4/\mu L$
Hb	12.30	g/dL
Ht	37.30	%
PLT	13.30	$\times 10^4/\mu L$
PT (%)	81.90	%
Serum chemistry		
TP	9.70	g/dL
ALB	3.60	g/dL
T-Bil	1.00	mg/dL
AST	418.00	U/L
ALT	366.00	U/L
ALP	371.00	U/L
γ-GT	102.00	U/L
LD	388.00	U/L
BUN	13.40	mg/dL
Cre	0.65	mg/dL
CRP	0.02	mg/dL
IgA	605.00	mg/dL
IgM	795.00	mg/dL
IgG	3481.00	mg/dL
ANA	80	
ASMA	640	
AMA	< 20	
HAV-IgM	Negative	
HEV-IgA	Negative	
HBs-Ag	Negative	
HBs-Ab	Negative	
HBc-Ab	Positive	
HBV-DNA	< 2.1	Logcopy/mL
HCV-Ab	Positive	
HCV-RNA	< 1.2	LogIU/mL
CMV-IgM	Negative	
CMV-IgG	Positive	
VCA-IgM	Negative	
VCA-IgG	Positive	
EBNA	Positive	
HLA	DR4	

WBC: White blood cell; RBC: Red blood cell; Hb: Hemoglobin; Ht: Hematocrit; PLT: Platelet; PT: Prothrombin time; TP: Total protein; ALB: Albumin; T-Bil:

Total-bilirubin; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; γ-GT: γ-Glutamyl transpeptidase; LD: Lactate dehydrogenase; BUN: Blood urea nitrogen; CRP: C reactive protein; ANA: Antinuclear antibody; ASMA: Antismooth muscle antibody; AMA: Antimitochondrial antibody; HAV: Hepatitis A virus; HEV: Hepatitis E virus; VCA: Viral capsid antigen; HCV: Hepatitis C virus; EBNA: Epstein-Barr virus nuclear antigen; HLA: Human leukocyte antigen.

pattern and 1:640, respectively, whereas the antimitochondrial antibody (AMA) was negative. Notably, ANA and ASMA were negative before the start of the DAA regimen, yet the titers of both antibodies gradually increased during and after treatment (Table 2).

Imaging examinations

Contrast-enhanced computed tomography revealed no abnormal findings at the time of exacerbation. Liver biopsy examination showed inflammatory cell infiltration mainly composed of lymphocytes and plasma cells in the portal and lobular areas and severe interface hepatitis with rosette formation (Figure 1A and B).

FINAL DIAGNOSIS

The definite diagnosis of AIH was made according to the International Diagnostic Criteria and Simplified Criteria for AIH, based on laboratory tests and liver biopsy findings, with scores of 18 and 8 points, respectively.

TREATMENT

After the AIH diagnosis, a daily 20 mg (0.5 mg/kg) dose of prednisolone was started. Serum AST, ALT, and IgG levels decreased significantly and reached normal limits (Figure 2). Daily 600 mg ursodeoxycholic acid (UDCA) doses were administered along with tapering of the prednisolone dose. Remission of AIH and normalization of serum AST, ALT, and IgG levels were maintained with daily doses of prednisolone (2.5 mg) and UDCA (600 mg).

OUTCOME AND FOLLOW-UP

The patient was still receiving treatment with 2.5 mg prednisolone and 600 mg UDCA three years after achieving SVR. Although laboratory examinations showed no elevation of serum liver enzymes, IgG, or IgG 4, magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography revealed diffuse stenosis extending from the intrahepatic bile duct to the common hepatic duct, and dilation of the peripheral bile duct (Figure 3). A second liver biopsy was performed, which showed improvement of the interface hepatitis, yet massive infiltration of lymphocytes and plasma cells and proliferation of interlobular bile ducts in the portal triad area (Figure 1C and D). She was diagnosed with PSC based on the 2016 diagnostic criteria.

DISCUSSION

Most cases of HCV infection do not present spontaneous remission and evolve to chronic viral hepatitis, which can lead to cirrhosis and hepatocellular carcinoma. Persistent HCV infection alters innate and adaptive immune responses functionally and phenotypically, including natural killer (NK) cell dysfunction and reduced NK cell diversity[9], viral escape mutation[10], HCV-specific CD8 T cell exhaustion, increased regulatory CD4 T cells (Treg), and deletion of HCV-specific CD4 T cells[11-13]. T cell exhaustion occurs due to ongoing antigen stimulation and is characterized by the loss of effector functions and increased expression of inhibitory markers[9,14,15]. Recently, DAAs have enabled almost all patients to completely eliminate HCV and achieve SVR. The effect of DAAs on rapid viral clearance is being investigated worldwide. Several reports have revealed that DAA therapy rapidly restores some adaptive immune functions, such as relative Treg reduction and HCV-specific T-cell function recovery[16,17]. In patients with AIH, a low number of functional CD4+ Tregs has been reported[18]. The restoration of the immune function may disrupt immune tolerance and cause autoimmune diseases.

Mucosal-associated invariant T (MAIT) cells have recently gathered attention as possible factors associated with autoimmune disease[19]. MAIT cells are an innate-like T cell subset that comprises 5%-10% peripheral T cells and approximately 12%-50% of T cells in the liver and gastrointestinal tract[20,21]. The dominance of MAIT cells in the liver indicates their potential essential role in the pathogenesis of chronic HCV infection[22]. Among patients infected with HCV, the number and function of intrahepatic and peripheral MAIT cells were significantly reduced compared to those in healthy controls[23]. Additionally, impaired peripheral MAIT cells do not recover after successful antiviral therapy; in contrast, the number of MAIT cells in the liver increased after therapy[22]. In multiple sclerosis, an autoimmune disease, MAIT cells are reportedly reduced in the peripheral blood and can be detected in most of the cerebrospinal fluid[24]. Therefore,

Table 2 Blood test results (antinuclear antibody and antismooth muscle antibody)

Blood test	ANA	ASMA
Before DAAs (SOF/LDV) therapy	< 20	< 20
After DAAs (SOF/LDV) therapy	40	20
SVR 12	40	160
SVR 24	80	640

ANA: Antinuclear antibody; ASMA: Antismooth muscle antibody; DAA: Direct antiviral agent; SOF: Sofosbuvir; LDV: Ledipasvir; SVR: Sustained virological response.

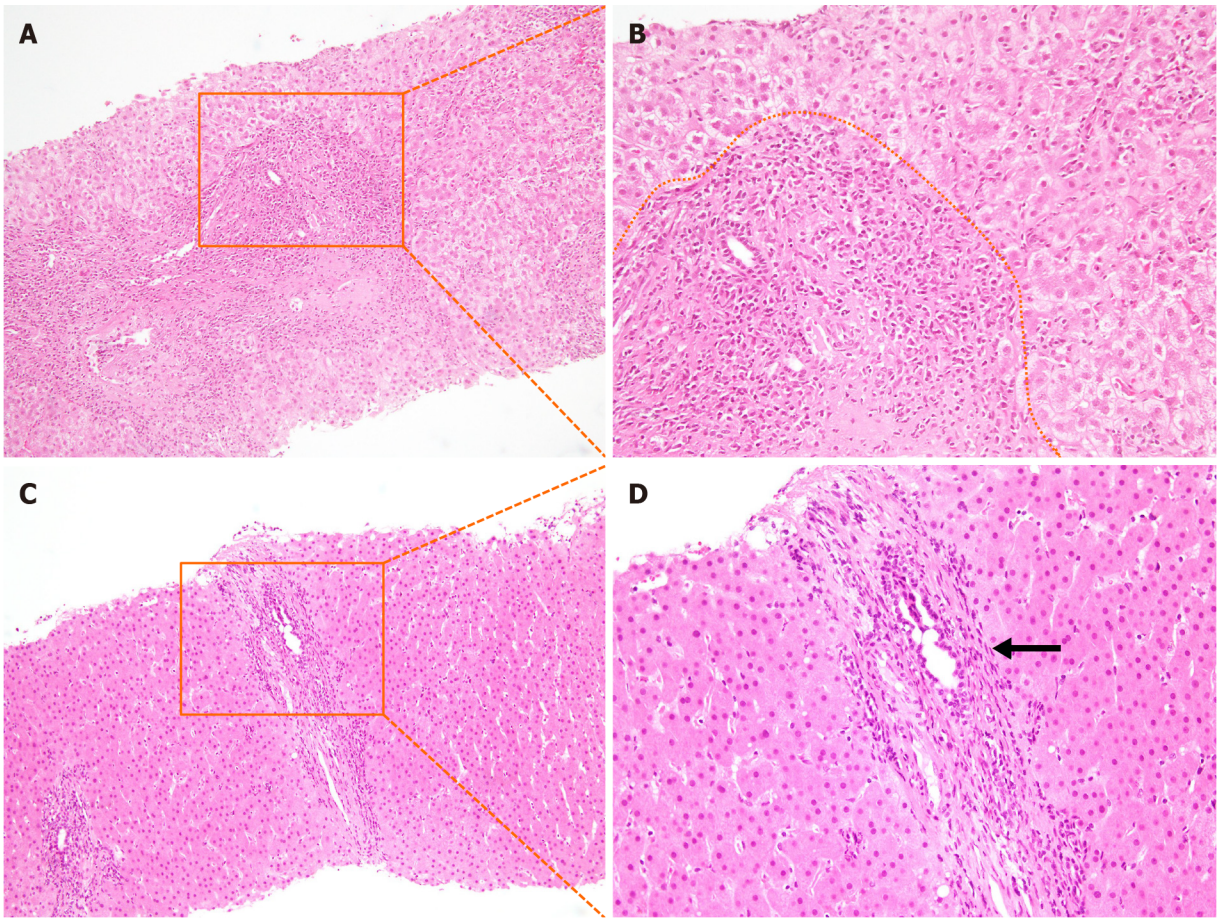

Figure 1 Initial and second liver biopsy. A and B: The initial liver biopsy showing inflammatory cell infiltration mainly composed of lymphocytes and plasma cells in the portal and lobular areas, and severe interface hepatitis with rosette formation. Hematoxylin and eosin staining (HE: A, × 100; B, × 200); C and D: A second liver biopsy shows improvement of the interface hepatitis, yet a massive infiltration of lymphocytes and plasma cells is noted. B and D are magnified images of the yellow square in A and C, the black arrow shows the proliferation of interlobular bile ducts in the portal triad area (HE: C, × 100; D, × 200).

activation of MAIT cells in lesions may facilitate inflammation and fibrosis in autoimmune diseases.

Notably, human leukocyte antigen (HLA)-DR4 was positive in our case. Classical (type 1) AIH is strongly associated with the HLA-DR3 (HLA-DRB1*03) and HLA-DR4 (HLA-DRB1*04), whereas the type 2 disease is associated with the HLA-DRB1*07 and HLA-DRB1*03[25,26]. In Japan, where HLA-DR3 is rare, AIH is primarily associated with the HLA-DR4 serotype[27]. Genetic and environmental factors are involved in the development of AIH[28]. In our case, HLA-DR4 as a genetic factor and various levels of immune activation associated with the elimination of HCV due to DAA treatment as an environmental factor likely induced an immune response to liver autoantigens, leading to AIH onset. Further studies are required to elucidate these underlying mechanisms.

Only four cases of AIH that developed after DAA treatment have been reported in the English literature, including our case[29-31] (Table 3). All identified patients were females, with a median age of 76 years. HLA-DR4 was positive in our case; however, such was not identified in the other cases. Three cases had HCV genotype Ib and one had serotype I. Only one case had a coexisting autoimmune disease, namely, idiopathic thrombocytopenic purpura with CHC infection[31]. Although reports of HCV and AIH overlap exist, the four cases have no findings that suggested AIH before DAA

Table 3 Four cases of autoimmune hepatitis development following direct antiviral agent treatment

Ref.	Age	Sex	HLA-DR4	Autoimmune disease	Genotype	DAA	Onset	Treatment	Follow up
Matsumoto *et al* [29], 2018	81	Female	Negative	None	1 (serotype)	EBR/GZR	2 months	PSL	Improvement
Covini *et al*[31], 2018	72	Female	NA	ITP	1b	SOF/LDV	2 wk	PSL	Improvement
Montón *et al*[30], 2020	72	Female	NA	None	1b	SOF/LDV	3 yr	PSL	Improvement
Our case	80	Female	Positive	None	1b	SOF/LDV	9 months	PSL + UDCA	Development of PSC

DAA: Direct antiviral agent; EBR/GZR: Elbasvir/Grazoprevir; HLA: Human leukocyte antigen; ITP: Idiopathic thrombocytopenic purpura; PSC: Primary sclerosing cholangitis; PSL: Prednisolone; SOF/LDV: Sofosbuvir/Ledipasvir; UDCA: Ursodeoxycholic acid.

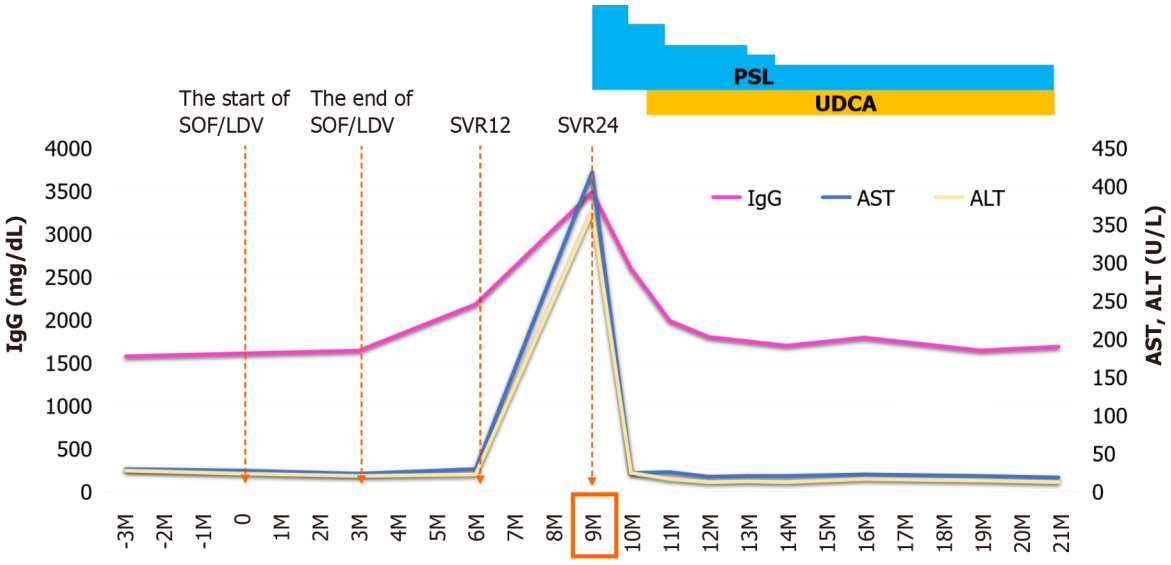

Figure 2 Aspartate aminotransferase, alanine aminotransferase, and IgG levels over time. The figure shows that aspartate aminotransferase (AST), alanine aminotransferase (ALT), and IgG are elevated after direct acting antiviral agents therapy. After the start of prednisolone, AST, ALT, and IgG decrease significantly and approach the normal limits. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; LDV: Ledipasvir; PSL: Prednisolone; SOF: Sofosbuvir; SVR: Sustained virological response; UDCA: Ursodeoxycholic acid.

treatment initiation. In our case, ANA and ASMA were negative before the start of the DAA regimen, and the titers of both antibodies gradually increased during and after treatment. Therefore, the DAA treatment is thought to have triggered the development of AIH. Three cases were treated with SOF/LDV[30,31], and one case was treated with elbasvir and grazoprevir[29]. Laboratory examinations showed an increase in ANA in all cases and an increase in ASMA in two cases[30]. IgG levels were elevated in three cases[29,30]. All patients underwent liver biopsy, which revealed interface hepatitis and infiltration of various inflammatory cells, including plasma cells, in the portal zonal areas. Serological and histological findings suggested the development of AIH. All patients received prednisolone, which led to improvements in serum AST, ALT, and IgG levels. Furthermore, serum HCV RNA was continuously undetectable in all cases. Only in our case, PSC was diagnosed 3 years after prednisolone treatment. Despite the small number of cases, immunosuppressive therapy is likely to be effective when AIH develops after HCV treatment.

Our case suggested that AIH and PSC development may be attributed to the rapid changes in immune function induced by DAA treatment. However, it was not possible to directly elucidate the mechanism underlying the association in this report. Therefore, accumulation of similar cases to clarify the mechanism is required.

CONCLUSION

Studies on antiviral therapy for HCV, highlighting the safety and effectiveness of DAA regimens, have reported sporadic episodes of adverse effects associated with immune dysregulation. We encountered a rare case of AIH with PSC that developed after DAA treatment. The potential risk of developing autoimmune liver diseases after DAA treatment owing

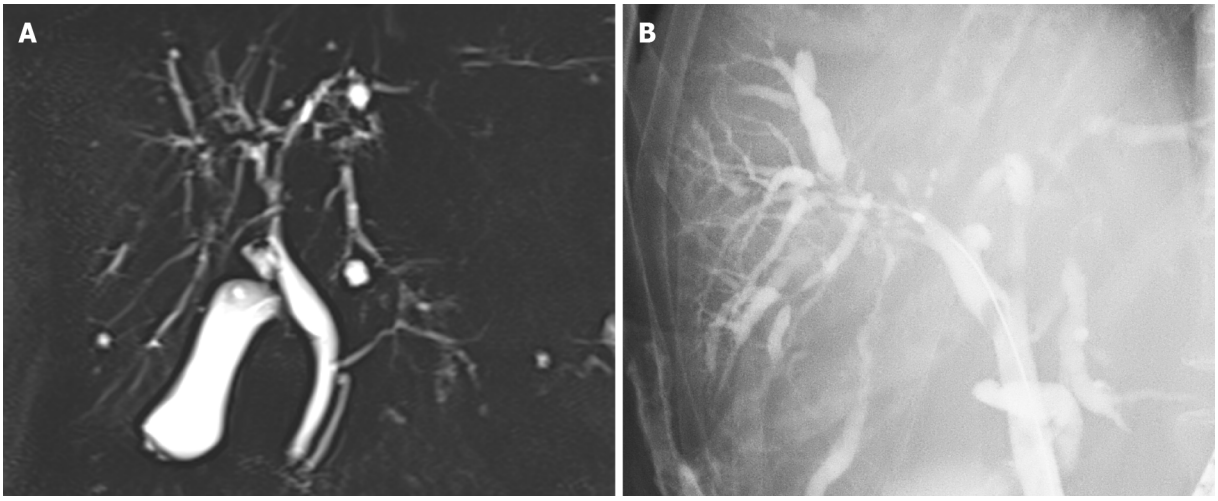

Figure 3 Magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography. A: Magnetic resonance cholangiopancreatography; B: Endoscopic retrograde cholangiopancreatography shows diffuse stenosis extending from the intrahepatic bile duct to the common hepatic duct, with dilation of the peripheral bile duct.

to the restoration of host immunity associated with rapid viral clearance should be considered. Further studies are necessary to clarify the frequency and mechanism of autoimmune liver diseases following DAA treatment.

FOOTNOTES

Author contributions: Morihisa Y drafted the manuscript; Chung H, Towatari S, Yamashita D, and Inokuma T contributed to the critical revision of the manuscript; all authors have read and approved the final manuscript.

Informed consent statement: Informed written consent was obtained from the patients for the publication of this report and any accompanying images.

Conflict-of-interest statement: All authors declare that they have no conflicts of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: Japan

ORCID number: Yoshiki Morihisa 0000-0002-8636-2488; Hobyung Chung 0000-0003-1112-6533.

S-Editor: Chen YL
L-Editor: A
P-Editor: Yuan YY

REFERENCES

1 **Polaris Observatory HCV Collaborators**. Global change in hepatitis C virus prevalence and cascade of care between 2015 and 2020: a modelling study. *Lancet Gastroenterol Hepatol* 2022; **7**: 396-415 [PMID: 35180382 DOI: 10.1016/S2468-1253(21)00472-6]
2 **European Association for the Study of the Liver**. EASL Recommendations on Treatment of Hepatitis C 2018. *J Hepatol* 2018; **69**: 461-511 [PMID: 29650333 DOI: 10.1016/j.jhep.2018.03.026]
3 **Pawlotsky JM**, Feld JJ, Zeuzem S, Hoofnagle JH. From non-A, non-B hepatitis to hepatitis C virus cure. *J Hepatol* 2015; **62**: S87-S99 [PMID: 25920094 DOI: 10.1016/j.jhep.2015.02.006]
4 **Manns MP**, Wedemeyer H, Cornberg M. Treating viral hepatitis C: efficacy, side effects, and complications. *Gut* 2006; **55**: 1350-1359 [PMID: 16905701 DOI: 10.1136/gut.2005.076646]
5 **European Association for the Study of the Liver**. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. *J Hepatol* 2011; **55**: 245-264 [PMID: 21371579 DOI: 10.1016/j.jhep.2011.02.023]

6 **Waziry R**, Hajarizadeh B, Grebely J, Amin J, Law M, Danta M, George J, Dore GJ. Hepatocellular carcinoma risk following direct-acting antiviral HCV therapy: A systematic review, meta-analyses, and meta-regression. *J Hepatol* 2017; **67**: 1204-1212 [PMID: 28802876 DOI: 10.1016/j.jhep.2017.07.025]

7 **Herzer K**, Gerken G, Kroy D, Tacke F, Plewe J, Eurich D, Spengler U, Strassburg CP, Welker MW, Pischke S, Sterneck M, Mehrabi A, Weiss KH, Herber A, Berg T, Zimmermann T, Galle PR, Heinzow H, Schmidt H, Markova A, Serfert Y, Manns MP, Zeuzem S, Wedemeyer H. Impact of direct-acting antiviral therapy on the need for liver transplantation related to hepatitis C in Germany. *J Hepatol* 2018; **69**: 982-984 [PMID: 30089577 DOI: 10.1016/j.jhep.2018.07.001]

8 **Wedemeyer H**, Khera T, Strunz B, Björkström NK. Reversal of Immunity After Clearance of Chronic HCV Infection-All Reset? *Front Immunol* 2020; **11**: 571166 [PMID: 33133084 DOI: 10.3389/fimmu.2020.571166]

9 **Björkström NK**, Strunz B, Ljunggren HG. Natural killer cells in antiviral immunity. *Nat Rev Immunol* 2022; **22**: 112-123 [PMID: 34117484 DOI: 10.1038/s41577-021-00558-3]

10 **Salimi Alizei E**, Hofmann M, Thimme R, Neumann-Haefelin C. Mutational escape from cellular immunity in viral hepatitis: variations on a theme. *Curr Opin Virol* 2021; **50**: 110-118 [PMID: 34454351 DOI: 10.1016/j.coviro.2021.08.002]

11 **Shoukry NH**. Hepatitis C Vaccines, Antibodies, and T Cells. *Front Immunol* 2018; **9**: 1480 [PMID: 30002657 DOI: 10.3389/fimmu.2018.01480]

12 **Shuai Z**, Leung MW, He X, Zhang W, Yang G, Leung PS, Eric Gershwin M. Adaptive immunity in the liver. *Cell Mol Immunol* 2016; **13**: 354-368 [PMID: 26996069 DOI: 10.1038/cmi.2016.4]

13 **Kubes P**, Jenne C. Immune Responses in the Liver. *Annu Rev Immunol* 2018; **36**: 247-277 [PMID: 29328785 DOI: 10.1146/annurev-immunol-051116-052415]

14 **Utzschneider DT**, Legat A, Fuertes Marraco SA, Carrié L, Luescher I, Speiser DE, Zehn D. T cells maintain an exhausted phenotype after antigen withdrawal and population reexpansion. *Nat Immunol* 2013; **14**: 603-610 [PMID: 23644506 DOI: 10.1038/ni.2606]

15 **Zheng K**, Zheng X, Yang W. The Role of Metabolic Dysfunction in T-Cell Exhaustion During Chronic Viral Infection. *Front Immunol* 2022; **13**: 843242 [PMID: 35432304 DOI: 10.3389/fimmu.2022.843242]

16 **Luxenburger H**, Neumann-Haefelin C, Thimme R, Boettler T. HCV-Specific T Cell Responses During and After Chronic HCV Infection. *Viruses* 2018; **10** [PMID: 30453612 DOI: 10.3390/v10110645]

17 **Ghosh A**, Romani S, Kottilil S, Poonia B. Lymphocyte Landscape after Chronic Hepatitis C Virus (HCV) Cure: The New Normal. *Int J Mol Sci* 2020; **21** [PMID: 33050486 DOI: 10.3390/ijms21207473]

18 **Lapierre P**, Lamarre A. Regulatory T Cells in Autoimmune and Viral Chronic Hepatitis. *J Immunol Res* 2015; **2015**: 479703 [PMID: 26106627 DOI: 10.1155/2015/479703]

19 **Toubal A**, Nel I, Lotersztajn S, Lehuen A. Mucosal-associated invariant T cells and disease. *Nat Rev Immunol* 2019; **19**: 643-657 [PMID: 31308521 DOI: 10.1038/s41577-019-0191-y]

20 **Franciszkiewicz K**, Salou M, Legoux F, Zhou Q, Cui Y, Bessoles S, Lantz O. MHC class I-related molecule, MR1, and mucosal-associated invariant T cells. *Immunol Rev* 2016; **272**: 120-138 [PMID: 27319347 DOI: 10.1111/imr.12423]

21 **Godfrey DI**, Uldrich AP, McCluskey J, Rossjohn J, Moody DB. The burgeoning family of unconventional T cells. *Nat Immunol* 2015; **16**: 1114-1123 [PMID: 26482978 DOI: 10.1038/ni.3298]

22 **Bolte FJ**, O'Keefe AC, Webb LM, Serti E, Rivera E, Liang TJ, Ghany M, Rehermann B. Intra-Hepatic Depletion of Mucosal-Associated Invariant T Cells in Hepatitis C Virus-Induced Liver Inflammation. *Gastroenterology* 2017; **153**: 1392-1403.e2 [PMID: 28780074 DOI: 10.1053/j.gastro.2017.07.043]

23 **Beudeker BJB**, van Oord GW, Arends JE, Schulze Zur Wiesch J, van der Heide MS, de Knegt RJ, Verbon A, Boonstra A, Claassen MAA. Mucosal-associated invariant T-cell frequency and function in blood and liver of HCV mono- and HCV/HIV co-infected patients with advanced fibrosis. *Liver Int* 2018; **38**: 458-468 [PMID: 28792648 DOI: 10.1111/liv.13544]

24 **Miyazaki Y**, Miyake S, Chiba A, Lantz O, Yamamura T. Mucosal-associated invariant T cells regulate Th1 response in multiple sclerosis. *Int Immunol* 2011; **23**: 529-535 [PMID: 21712423 DOI: 10.1093/intimm/dxr047]

25 **Terziroli Beretta-Piccoli B**, Mieli-Vergani G, Vergani D. Autoimmmune hepatitis. *Cell Mol Immunol* 2022; **19**: 158-176 [PMID: 34580437 DOI: 10.1038/s41423-021-00768-8]

26 **Bittencourt PL**, Goldberg AC, Cançado EL, Porta G, Laudanna AA, Kalil J. Different HLA profiles confer susceptibility to autoimmune hepatitis type 1 and 2. *Am J Gastroenterol* 1998; **93**: 1394-1395 [PMID: 9707090 DOI: 10.1111/j.1572-0241.1998.1394a.x]

27 **Furumoto Y**, Asano T, Sugita T, Abe H, Chuganji Y, Fujiki K, Sakata A, Aizawa Y. Evaluation of the role of HLA-DR antigens in Japanese type 1 autoimmune hepatitis. *BMC Gastroenterol* 2015; **15**: 144 [PMID: 26489422 DOI: 10.1186/s12876-015-0360-9]

28 **Chen J**, Eslick GD, Weltman M. Systematic review with meta-analysis: clinical manifestations and management of autoimmune hepatitis in the elderly. *Aliment Pharmacol Ther* 2014; **39**: 117-124 [PMID: 24261965 DOI: 10.1111/apt.12563]

29 **Matsumoto K**, Kikuchi K, Kajiyama Y, Takano Y, Mabuchi M, Doi S, Sato K, Miyakawa H, Yasuda I. Development of Autoimmune Hepatitis during Direct-acting Antiviral Therapy for Chronic Hepatitis C Virus Infection. *Intern Med* 2018; **57**: 2669-2673 [PMID: 29709942 DOI: 10.2169/internalmedicine.0613-17]

30 **Montón C**, Escudero MªD, Pascual I. The development of type-1 autoimmune hepatitis after chronic hepatitis C (HCV) clearance by direct-acting antivirals (DAA). *Rev Esp Enferm Dig* 2020; **112**: 664-665 [PMID: 32686431 DOI: 10.17235/reed.2020.6785/2019]

31 **Covini G**, Bredi E, Badalamenti S, Roncalli M, Aghemo A, Colombo M. Autoimmune Hepatitis During Ledipasvir/Sofosbuvir Treatment of Hepatitis C: A Case Report. *Hepatol Commun* 2018; **2**: 1179-1183 [PMID: 30288473 DOI: 10.1002/hep4.1248]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: office@baishideng.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com