



Acute-on-chronic liver failure induced by antiviral therapy for chronic hepatitis C: A case report

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Specialty type: Infectious diseases

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, B

Grade C (Good): 0

Grade D (Fair): D

Grade E (Poor): 0

P-Reviewer: Dabbous H, Egypt;
Korkmaz P, Turkey

Received: July 31, 2023

Peer-review started: July 31, 2023

First decision: August 17, 2023

Revised: August 30, 2023

Accepted: September 26, 2023

Article in press: September 26, 2023

Published online: October 26, 2023



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Abstract

BACKGROUND

There have been no reports of acute-on-chronic liver failure (ACLF) during treatment of chronic hepatitis C (CHC) with direct-acting antivirals (DAAs).

CASE SUMMARY

We report a 50-year-old male patient with CHC. The patient sought medical attention from the Department of Infectious Diseases at our hospital due to severe yellowing of the skin and sclera, which developed 3 mo previously and attended two consecutive hospitals without finding the cause of liver damage. It was not until 1 mo ago that he was diagnosed with CHC at our hospital. After discharge, he was treated with DAAs. During treatment, ACLF occurred, and timely measures such as liver protection, enzyme lowering, anti-infective treatment, and suppression of inflammatory storms were implemented to control the condition.

CONCLUSION

DAA drugs significantly improve the cure rate of CHC. However, when patients have factors such as autoimmune attack, coinfection, or unclear hepatitis C virus genotype, close monitoring is required during DAA treatment.

Key Words: Chronic hepatitis C; Acute-on-chronic liver failure; Direct acting antivirals; Sofosbuvir-velpatasvir; Case report

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Core Tip: The advent of direct-acting antivirals (DAAs) for chronic hepatitis C (CHC) has improved the rate of sustained virology response, resulting in clinical cure of CHC. We report a rare case of CHC where the patient developed acute-on-chronic liver failure during DAA therapy. Based on comprehensive analysis, the genotype of hepatitis C virus in this patient was unclear, and he was in an autoimmune hyperimmune state at the time and was coinfecting with bacteria. When CHC is combined with the above conditions, close monitoring should be carried out during treatment to avoid a poor prognosis.

Citation: Zhong JL, Zhao LW, Chen YH, Luo YW. Acute-on-chronic liver failure induced by antiviral therapy for chronic hepatitis C: A case report. *World J Clin Cases* 2023; 11(30): 7463-7468

URL: <https://www.wjgnet.com/2307-8960/full/v11/i30/7463.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v11.i30.7463>

INTRODUCTION

Hepatitis C is an infectious disease caused by hepatitis C virus (HCV). HCV exposure can cause acute hepatitis C, which is defined as the 6-mo period after HCV exposure. Patients who fail to spontaneously clear the virus during acute infection develop persistent infection, which can cause liver inflammation and other serious liver damage. Chronic hepatitis C (CHC) occurs in 50%-80% of patients[1], and 5%-30% of CHC patients develop liver cirrhosis, liver failure and even hepatocellular carcinoma within 20-30 years[2]. Therefore, early diagnosis and treatment of CHC are very important. Over the past 10 years, direct-acting antivirals (DAAs) have revolutionized HCV treatment, increasing cure rates from < 50% to > 95%. However, we report a CHC patient in our hospital who developed acute-on-chronic liver failure (ACLF) during DAA treatment.

CASE PRESENTATION

Chief complaints

A 50-year-old male patient presented with yellow staining of the skin and sclera, poor appetite and fatigue for 1 wk.

History of present illness

Symptoms started 1 wk before presentation with yellow staining of the skin and sclera, poor appetite and fatigue.

History of past illness

Three months ago, due to yellow staining of the skin and sclera, the patient went to two tertiary hospitals for consecutive visits. Examination showed severe liver damage but the following causes were excluded: Viral hepatitis (negative for hepatitis A, B, C and E); autoimmune liver diseases (negative for autoimmune hepatitis antibody 1, autoimmune hepatitis antibody 2, immunoglobulin quantification and IgG4); [negative for rubella virus, Epstein-Barr virus (EBV), cytomegalovirus (CMV), and herpesvirus]; *Toxoplasma gondii* and hepatolenticular degeneration (negative for ceruloplasmin). Endoscopy showed chronic nonatrophic gastritis. Abdominal ultrasound showed rough echo in liver parenchyma. Upper abdominal magnetic resonance imaging (MRI) showed hepatitis or liver injury, reactive cholecystitis, and splenomegaly. Liver pathological biopsy showed that liver cells were edematous, focal necrosis, scattered lymphocytes, neutrophil infiltration, and chronic inflammatory cell infiltration in the portal area with fibrosis, in line with chronic hepatitis grade 2 and stage 1. Bilirubin level gradually increased after conservative treatment with drugs, and the patient was admitted to our hospital. The admission examination showed that the total bilirubin was increased to 389.5 mmol/L, hepatitis C antibody was weakly positive, and hepatitis C RNA load was 2.281×10^3 IU/mL. The HCV genotype could not be typed due to low viral load. The patient's other examinations revealed no abnormalities. He was diagnosed with severe CHC and received medication (glycyrrhetic acid monoamine S 160 mg ivgtt qd, Shuganning injection 10 mL ivgtt qd, ursodeoxycholic acid capsule 250 mg po tid) and artificial liver treatment (plasma exchange + double plasma molecular adsorption system) on March 31 and April 2, 2022, respectively. The patient was discharged on April 18, 2022 with improved liver function. After discharge, he was treated with sofosbuvir-velpatasvir 400:100 mg one tablet/d.

Personal and family history

The patient had smoked 10 cigarettes/d for > 20 years, and had no history of drinking, drug use, blood transfusion, or family history of CHC.

Physical examination

On physical examination, the vital signs were as follows: body temperature, 36.2°C; blood pressure, 127/78 mmHg; heart rate, 88 bpm; respiratory rate, 20 breaths/min. He also had severe yellowing of the whole body skin and sclera. Moist rales were heard in both lungs on auscultation.

Laboratory examinations

HCV antibody was still positive, HCV RNA was < 50 IU/mL, and the genotype still could not be typed. Liver function parameters were: Alanine aminotransferase (ALT) 499 U/L, aspartate aminotransferase (AST) 935 U/L, AST/ALT 2.01, alkaline phosphatase 316 U/L, γ -glutamyl transferase 203 U/L, total bilirubin 337 μ mol/L, direct bilirubin 176.6 μ mol/L, total protein 62.7 g/L, albumin 42 g/L, globulin 21 g/L, and prealbumin 67 mg/L. Coagulation function was: International normalized ratio (INR) 1.12 and prothrombin time activity (PTA) 82%. Routine blood analysis showed the following: White blood cells (WBCs) 10.5×10^9 /L, neutrophils 5.36×10^9 /L, lymphocytes 3.46×10^9 /L, hemoglobin 151 g/L, and platelets 504×10^9 /L.

Imaging examinations

Upper abdominal MRI (plain scan + enhancement + hepatobiliary pancreatic MRI water imaging) showed liver cirrhosis, splenomegaly, portal hypertension (maximum diameter of main portal vein approximately 15 mm) and suspected cholecystitis. Multiple lymph nodes in the abdominal cavity and retroperitoneum were observed. Chest computed tomography showed bilateral lower lobe pneumonia.

Further diagnostic work-up

Hepatitis B surface antigen, hepatitis virus A and E antibodies, ceruloplasmin, transferrin saturation, EBV DNA, CMV DNA, α -fetoprotein and thyroid function were all negative. Autoimmune hepatitis antibodies show positivity for anti-nuclear and anti-mitochondrial antibody M2, immunoglobulin quantitative: negative. Samples were sent to Jinyu Medical Test Center to examine the eight items of autoimmune hepatitis antibody, among which anti-mitochondrial subtype-2 antibody was positive. Dynamic monitoring of liver function, coagulation function, and routine blood changes during hospitalization are shown in Table 1.

FINAL DIAGNOSIS

Combined with the patient's medical history, the final diagnosis was: ACLF, CHC and pulmonary infection.

TREATMENT

The patient was admitted to the hospital on April 27, 2022. In order to rule out drug factors, sofosbuvir and velpatasvir were discontinued. The patient received a hepatoprotective treatment (magnesium isopyrrrhizinate injection 150 mg ivgtt qd, Shuganning injection 10 mL ivgtt qd, ursodeoxycholic acid capsule 250 mg po tid) and anti-infective treatment (ceftazidime 2 g ivgtt q8h). However, on April 30, the patient's bilirubin continued to rise to 415.7 mmol/L, PTA continued to decrease to 33.1%, and blood cell counts were WBCs 13.91×10^9 /L, atypical lymphocytes 6%, neutrophils 9.88×10^9 /L, and lymphocytes 2.64×10^9 /L. The patient had depression, the gastrointestinal symptoms worsened, and hiccups occurred. ACLF was considered. Therefore, the antibiotics were adjusted to piperacillin-tazobactam sodium 3.75 g ivgtt q8h to continue antibacterial treatment. Aciclovir 0.25 g ivgtt q8h antiviral treatment, and hormones (methylprednisolone 40 mg qd) were given to suppress immunity, over a course of 5 d. Simultaneously, artificial liver (plasma exchange + double plasma molecular adsorption system) adjuvant therapy was administered. On May 5, routine blood examination showed normal results, and EBV and CMV DNA were negative. As the patient's atypical lymphocytes only appeared once, it was considered secondary to immune disorders. Therefore, ganciclovir and piperacillin-tazobactam sodium were discontinued, but hepatoprotective treatment was continued. Re-examination on May 17 showed that liver function parameters were ALT 27 U/L, AST 36 U/L, and total bilirubin 77.4 μ mol/L; therefore, the patient was discharged from hospital on May 19, 2022. He continued to take sofosbuvir-velpatasvir 400: 100 mg 1 tablet/d for antiviral treatment.

OUTCOME AND FOLLOW-UP

The outpatient department checked that the patient's liver function was normal on June 23, 2022, and he received antiviral treatment until August 20. Follow-up to March 1, 2023 showed that HCV RNA was consistently below the detection limit, liver function, routine blood examination and α -fetoprotein were normal. Abdominal ultrasound showed that the light spots on the liver had thickened, instantaneous elastic imaging of the liver showed a hardness of 15.7 kPa and fat attenuation of 247 dB/m. Unexpectedly, autoimmune hepatitis and mitochondrial antibodies were negative.

DISCUSSION

Sofosbuvir-velpatasvir is a combined oral DAA. Sofosbuvir is a nucleotide analog NS5B polymerase inhibitor that inhibits viral replication by targeting key targets of RNA replication, while velpatasvir is a second-generation NS5A replication complex inhibitor with high antiviral activity against all HCV genotypes[3]. In noncirrhotic patients, the

Table 1 Laboratory results during hospitalization

	April 27	April 29	April 30	May 1	May 3	May 5	May 7	May 9	May 11	May 15	May 17
ALT (U/L)	495	917	859	372	176	110	61	51	47	34	27
AST (U/L)	935	1841	1176	323	90	45	28	34	49	38	36
ALP (U/L)	316	251	278	168	148	199	198	162	165	175	169
GGT (U/L)	203	110	121	58	52	66	64	83	83	85	78
TBIL ($\mu\text{mol/L}$)	337	335.1	415.7	255.1	155.1	132.9	116.8	158	150.9	101.8	77.4
ALB (g/L)	42	29.4	35	30.1	30.6	31.2	32.3	37.1	36.8	40.1	37.8
PTA (%)	82	40.8	33.1	26	67.5	110.3	135.1	150	139.3	110	-
PT-INR	1.12	1.82	2.20	2.78	1.24	0.94	0.85	0.78	0.84	0.95	-
WBC ($10^9/\text{L}$)	10.5	10.16	13.91	16.05	9.71	7.91	-	7.20	-	5.07	-
N ($10^9/\text{L}$)	5.36	5.28	9.88	11.88	7.19	5.06	-	4.61	-	3.19	-
L ($10^9/\text{L}$)	3.46	3.35	2.64	3.05	1.84	2.21	-	2.09	-	1.42	-
PLT ($10^{12}/\text{L}$)	504	455	639	529	482	418	-	311	-	330	-

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; GGT: γ -Glutamyl transferase; TBIL: Total bilirubin; ALB: Albumin; PTA: Prothrombin time activity; PT-INR: International normalized ratio; WBC: White blood cells; N: Neutrophil absolute value; L: Lymphocyte absolute value; PLT: Platelets.

sustained virological response rate (SVR) can reach 95% [4]. Even in patients with HCV-related decompensated cirrhosis, the SVR rate is > 80% [5]. The patient had no previous underlying diseases, and only took sofosbuvir-velpatasvir following the diagnosis of hepatitis C, without drug interaction. There is no pharmacokinetic basis for liver damage due to sofosbuvir-velpatasvir. The occurrence of ACLF during DAA treatment may be related to the following factors.

Autoimmunity

The emergence of autoimmune diseases may be related to viral infection, especially chronic viral infection. HCV infection has long been suspected to be associated with the development of autoimmune diseases, as demonstrated by cryoglobulinemia [6], and antineutrophil and smooth muscle actin are the most frequently detected autoantibodies [7]. The mechanisms by which these antibodies are produced are not fully understood, but HCV can trigger a B-lymphocyte-mediated immune response shortly after immune system activation. B-lymphocyte-driven humoral immunity produces specific antibodies that are unable to inactivate virus production and replication. Therefore, the continuous replication of HCV results in constant stimulation of B cells, which may lead to B-cell dysfunction and abnormal antibody production [8]. Alternatively, the presence of autoantibodies in HCV patients may be caused by chronic apoptotic hepatocytes. Viruses, unlike bacteria and fungi, cannot reproduce on their own and must use the host-cell processes to replicate as they cannot synthesize their own proteins [9,10]. However, the pathogenic mechanism of the virus and whether antibody production truly represents an independent autoimmune disease have not been fully elucidated. During the progression of CHC in the present case, autoimmune hepatitis antibodies showed positivity for anti-nuclear and anti-mitochondrial antibody M2, and atypical lymphocytes briefly appeared, which is rare in viral hepatitis [11]. Timely use of artificial liver replacement therapy and hormonal suppression of immunity can control disease development, indicating that autoimmunity plays an important role in the progression of hepatitis C to liver failure. When hepatitis C was cured, the above antibody test results were negative. It can be seen that these antibodies became negative after HCV clearance and were not an independent factor in liver function damage.

Bacterial infection

Bacterial infection may be another important reason for the rapid progression to ACLF in this case. The Asia Pacific Liver Research Association defines ACLF as an acute liver injury characterized by jaundice [serum bilirubin ≥ 5 mg/dL (85 $\mu\text{mol/L}$) and coagulation disorders (INR ≥ 1.5 or PTA < 40%), accompanied by clinical ascites and/or hepatic encephalopathy within 4 wk, with or without prior diagnosis of chronic liver disease/cirrhosis, and associated with a high 28-d mortality rate [12]. It is well known that bacterial infection is the most common precipitating factor of ACLF. One study demonstrated that the overall rate of ACLF related to bacterial infection was 48%, but the rate varied between geographical regions (38% in southern Europe, and 75% in the Indian subcontinent [13]). In particular, extensively drug resistant bacteria caused by spontaneous bacterial peritonitis, pneumonia, or infection are more frequently associated with ACLF. Timely empirical antibiotic treatment can change the balance between bacteria and the host, which is beneficial for bacterial clearance. Bacterial infection may be another important reason for rapid progression to ACLF. Our patient had a pulmonary infection during his second admission, and the condition was still progressing after ceftazidime treatment for the infection. The infection was gradually controlled by changing to piperacillin-tazobactam sodium, and the bacteria that may have caused the patient's pulmonary infection were sensitive to piperacillin-tazobactam sodium.

Refractory genotypes and resistance-associated variants

The primary goal of DAA therapy is SVR, which is defined as undetectable HCV RNA 12 wk after the end of antiviral therapy[14,15]. Viral resistance is a major cause of virological failure in patients receiving DAAs for CHC. Selection of the DAA regimen needs to take account of the drug resistance of the virus and HCV genotype. The proportion of patients with HCV genotype 3 was higher in the population who experienced DAA failure[16]. The current first-line drugs for hepatitis C, sofosbuvir and velpatasvir, have high antiviral activity and a high resistance barrier, and resistance-associated variants may exist in patients with HCV genotype 3 and other rare HCV genotypes. This patient was diagnosed with a low viral load and genotype was not detected during two consecutive hospitalizations and ACLF occurred during treatment. After active treatment, the patient improved and then continued to take antivirals. Follow-up showed that the treatment was effective, and no drug resistance had developed, but the genotype was still unknown. The global distribution of HCV genotypes is regional, with 1b being the main genotype in China. At the same time, there are significant population differences in the distribution of HCV genotypes, and transmission methods may also vary. Our patient has no history of blood transfusion or drug use. During antiviral treatment, liver failure occurred, and the genotype was not detected during two consecutive hospitalizations. We therefore speculate that this patient is rare in terms of the HCV genotypes, or there might be a seventh genotype that we do not know.

CONCLUSION

DAAs have significantly improved the cure rate of CHC. However, this case also suggests that there is still a risk of liver failure during CHC treatment with DAAs if there are factors such as autoimmunity, combined bacterial infection, or unclear HCV genotype, and timely therapy requires close monitoring.

FOOTNOTES

Author contributions: Zhong JL contributed to manuscript writing and editing, and data collection; Zhao LW contributed to data analysis; Chen YH and Luo YW contributed to supervision; all authors have read and approved the final manuscript.

Supported by the National Natural Science Foundation of China, No. 82160558; and Zunyi Science and Technology Fund.

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

Conflict-of-interest statement: The authors declare that they have no conflict of interest to disclose.

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).

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S-Editor: Yan JP

L-Editor: Webster JR

P-Editor: Xu ZH

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