Fibrosing Cholestatic Hepatitis in a Complicated Case of an Adult Recipient After Liver Transplantation: Diagnostic Findings and Therapeutic Dilemma

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Patient: Male, 66
Final Diagnosis: Fibrosing cholestatic hepatitis
Symptoms: Prolonged jaundice and intractable ascites
Medication: Steroid pulse therapy and direct-acting antivirals
Clinical Procedure: Liver transplantation
Specialty: Transplantology

Objective: Challenging differential diagnosis
Background: Hepatitis C recurrence is a serious matter after liver transplantation (LT). Approximately 10% of hepatitis C virus (HCV) positive recipients develop fibrosing cholestatic hepatitis (FCH). FCH rapidly results in graft loss. Currently, direct-acting antivirals (DAAs) are effective and safe for hepatitis C, even after LT. However, only a few cases of successfully treated FCH after LT have been reported. We present FCH in a complicated case with sepsis and portal flow obstruction after LT.

Case Report: A 66-year-old man underwent cadaveric LT. Liver function disorders were observed from post-operative day (POD) 22. Sepsis repeated on POD 38, 74, and 101. Steroid pulse therapy was given from POD 40 to 54. The infectious focus was surgically removed on POD 89. Interventional radiology for portal venous obstruction was completed on POD 96. To make a real-time diagnosis and to investigate the graft condition, repeat liver needle biopsies (LNBs) were taken. Although there was a combined impact of sepsis, portal flow decrease, and recurrent hepatitis C on graft failure, it was interesting that recurrent hepatitis C was consistently detectable from the first LNB. HCV-ribonucleic acid increased on POD 68. Liver function disorders peaked on POD 71 and 72. Jaundice peaked on POD 82. DAA induction was regrettably delayed because of a reluctance to introduce DAAs under conditions of graft dysfunction. DAAs were administered after hospital discharge.

Conclusions: A real-time and precise diagnosis based on histopathological examination and viral measurement is important for FCH treatment. Well-considered therapy with DAAs should be aggressively introduced for potentially fatal FCH after LT.

MeSH Keywords: Hepatitis • Hepatitis C • Liver Failure • Liver Transplantation

Abbreviations: IMV – inferior mesenteric vein; SMV – superior mesenteric vein

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Background

Chronic infection with hepatitis C virus (HCV) is the leading cause of death from liver disease and the leading indication for adult liver transplantation (LT) [1,2]. Reinfection of the allograft with HCV is inevitable in HCV-positive LT recipients, and hepatitis C occurs in 95% of LT recipients [1]. Recurrent hepatitis C is a cause of considerable morbidity and/or mortality [1,2].

Fibrosing cholestatic hepatitis (FCH) is rapidly progressive, and is an often fatal form of hepatitis B or C infection [1,2]. Approximately 10% of HCV-positive recipients will develop FCH after LT [1–3]. FCH is clinically characterized as marked jaundice with cholestatic hepatic dysfunction and high titers of viremia [1,2]. Pathologically, FCH manifests as marked hepatocyte swelling, cholestasis, periportal peritrabecular fibrosis with mild inflammation [1,2]. This progressive form of hepatitis C infection usually involves acute liver failure and rapidly results in graft loss [1–3].

A therapeutic goal of chronic HCV infection is a sustained virologic response (SVR) [4]. Historically, treatments for recurrent hepatitis C have been limited by their low rate of success and high rate of side effects [1,2]. Previous standard treatment for recurrent hepatitis C was combination therapy with pegylated interferon (IFN) and ribavirin, though this treatment induced a high rate of side effects, with a SVR rate of approximately 30% [1,2]. Currently, therapeutic strategies against HCV have dramatically improved with the recent availability of direct-acting antivirals (DAAs) [1,2,4]. Carefully selected combinations of DAAs are effective and safe even for patients with uncompensated cirrhosis or LT recipients [4]. DAAs have become the standard care in the pre-transplant setting [1,2,4], and moreover, have an expanding role for post-transplant recipients [1,2,4].

In 1964, Child and Turcotte published a classification to assess the operative risk in cirrhotic patients who recovered from variceal bleeding, and who were undergoing portosystemic shunt surgery. They considered five variables selected by clinical experience: ascites, encephalopathy, nutritional status, and serum levels of bilirubin and albumin, classifying patients as class A, B, or C in relation to best (A), moderate (B), or worst (C) prognosis [5]. In 1973, Pugh et al. used a modified version of this classification for patients undergoing surgical transection for esophageal varices. They replaced nutritional status with prothrombin time and assigned a score ranging from 1 to 3 for each variable [6]. Some DAAs should not be used in patients with Child C cirrhosis and/or severe renal impairment [4].

However, even though DAAs are currently available, only a few cases of successfully treated FCH after LT have been reported [7–11]. Here, we reported a case of successful treatment of potentially fatal FCH in a complicated case of an adult recipient after LT. Recipients usually show complicated clinical courses after LT. We report our diagnostic histopathological findings, and discussed the therapeutic dilemma in a case of potentially fatal FCH after LT.

Case Report

We present a complicated case of potentially fatal FCH after cadaveric LT. A 66-year-old man suffered from advanced liver cirrhosis and portal hypertension, caused by HCV (genotype Ib). He had a history of IFN therapy, but his response to IFN was poor. Imaging studies revealed venous thromboses in the portal venous (PV) trunk and splenic vein (SPV), and these showed confluence. The score of model for end-stage of liver disease was 11 points. He underwent deceased-donor LT. The donor’s age was young and the graft weight was sufficient. The graft-to-recipient weight ratio was 2.10. Ischemic preservation including cold storage was 559 minutes. The operative time was 618 minutes, and blood loss was significant (22,185 mL). The anhepatic phase was 282 minutes. Portal venous reconstruction is summarized in Figure 1. Portal inflow was performed by venous graft interposition from the recipient’s gastro-coelic trunk (GCT) to graft portal trunk, using a venous graft of the donor’s iliac vein. We performed a branch-patch anastomosis for hepatic arterial reconstruction, an end-to-end biliary anastomosis, and a piggy-back technique employed for the cava. The patient left the intensive care unit (ICU) at post-operative day (POD) 4, and an early post-operative course was uneventful. Thereafter, he developed repeated sepsis, portal inflow obstruction, and potentially fatal FCH. The clinical course is summarized in Figure 2. In this case, tacrolimus, mycophenolate mofetil (MMF), and prednisolone (PSL) were used. The trough level of tacrolimus is shown in Figure 2. To make a real-time diagnosis and investigate graft condition, the patient received a liver needle biopsy (LNB) at POD 22, 71, 82, 89, 96, and 179. Histopathological findings are summarized in Figures 3 and 4. Cytomegalovirus infection was observed at POD 22, and ganciclovir was given for 14 days. LNB was performed at POD 22 because disorders in conventional liver function tests were observed (Figure 3A). Tacrolimus was switched to a sustained-release agent from POD 31 onwards. On POD 38, sepsis occurred because of Klebsiella pneumoniae, and the focus of infection was intra-abdominal abscess near GCT (Figure 1). All immunosuppressants (tacrolimus, prednisolone, and mycophenolate mofetil) were stopped from POD 39 onwards. The abscess compressed the venous graft, and therefore the portal inflow continuously decreased. The patient stayed in the ICU from POD 39 to 47, and a percutaneous drain was placed into the intra-abdominal abscess on POD 39. Lavation through the abscess cavity was started from POD 60. From POD 40 to 54, steroid pulse therapy (SPT) with hydrocortisone was given for acute
Figure 1. Portal reconstruction. (A) Portal reconstruction was performed by venous graft interposition. The LGV as a developed collateral was ligated to prevent the steal phenomenon (red line). Intra-abdominal abscess nearly GCT (red dotted circle) seriously compressed the venous graft, and therefore portal inflow continuously decreased. (B) Multiple thromboses were confirmed in the PV trunk and SPV. Therefore, portal inflow was made by jumping a venous graft from the recipient’s GCT to the graft PV trunk, using a venous graft of the donor’s iliac vein. The LGV was ligated (red line). GCT – gastro-colic trunk; IMV – inferior mesenteric vein; LGV – left gastric vein; LPV – left portal vein; PV trunk – portal venous trunk; RPV – right portal vein; SMV – superior mesenteric vein; SPV – splenic vein.

Figure 2. Clinical course and immunosuppressive level after LT. The clinical course after LT is summarized. In this case, tacrolimus, methylprednisolone (MP), mycophenolate mofetil (MMF), and prednisolone (PSL) were used. The trough level of tacrolimus are also shown. AST – aspartate transaminase; ALT – alanine aminotransferase; BT – body temperature; CHDF – continuous hemodiafiltration; CMV – cytomegalovirus; CRP – C-reactive protein; GGT – γ-glutamyltransferase; HCV – hepatitis C virus; ICU – intensive care unit; IVR – Interventional radiology; LNB – liver needle biopsy; LT – liver transplantation; MMF – mycophenolate mofetil; MP – methylprednisolone; POD – post-operative day; PCT – procalcitonin; PLT – platelet; PSL – prednisolone; PT-INR – prothrombin time-international normalized ratio; RNA – ribonucleic acid; T-Bil – total bilirubin; WBC – white blood cell.
Figure 3. Histopathological findings of LNB specimens. Histopathological findings at PODs 22 (A), 64 (B), 71 (C, D), 82 (E), 89 (F), 96 (G) and 179 (H) are shown (hematoxylin and eosin staining, magnification ×200). Apoptotic hepatocytes were observed in all specimens (blue arrows). (A) Apoptotic hepatocytes were observed. (B) Hepatocyte ballooning was observed, especially around the hepatic vein. Inflammatory cells infiltrated into the periportal area. (C) Increasing numbers of inflammatory cells infiltrated into the periportal area, and piecemeal necrosis was observed. (D) Hepatocyte ballooning and cholestasis worsened. Apoptotic hepatocytes were increased. (E) Apoptotic hepatocytes were slightly decreased. Hepatocyte ballooning remained. (F) Hepatocyte ballooning was slightly improved, though inflammatory infiltration and piecemeal necrosis remained. (G) Hepatocyte ballooning was clearly decreased, although inflammatory infiltration and piecemeal necrosis remained. Bridging fibrosis was observed. (H) Apoptotic hepatocytes almost disappeared. Inflammatory infiltration at the periportal area was clearly decreased. Finding of chronic hepatitis C manifested as spotty and patchy necrosis (red arrows). Bridging fibrosis was observed. LNB – liver needle biopsy; POD – post-operative day.
respiratory distress syndrome (ARDS), and oral prednisone of 20 mg/day was continued from POD 55 to 74. Jaundice and ascites developed, and therefore cholangiography (POD 63), LNBs (POD 64 and 71) and hepatic venography (POD 72) were performed (Figure 3B–3D). Cytomegalovirus infection was detected again at POD 64, and ganciclovir was given again for 10 days. Although neither biliary obstruction nor out-flow block were observed, liver damage observed in the LNBs appeared to be potentially fatal (Figure 4A). HCV-ribonucleic acid (RNA) increased to 7.1 log IU/mL on POD 68. Serum levels of aspartate transaminase (AST), alanine aminotransferase (ALT), and γ-glutamyl transpeptidase (GGT) peaked on POD 71 and 72 (AST 157 U/L; ALT 311 U/L; GGT 269 U/L). The patient lapsed into septic shock again, and returned to the ICU at POD 74. Jaundice peaked on POD 82. Serum levels of total bilirubin (T-Bil) increased (19.2 mg/dL), and direct bilirubin was dominant. Bile discharge was serous but not golden brown. LNBs were performed on POD 82 and 89, and severe liver damage was still present (Figure 3E, 3F). The intra-abdominal abscess was removed under laparotomy on POD 89. Continuous hemodiafiltration was induced because of renal failure on POD 91. The decreased portal inflow remained, and therefore interventional radiology with balloon dilatation and stent placement was completed via percutaneous transhepatic approach on POD 96 (Figure 5). Thereafter, the portal inflow was markedly improved. Liver damage also improved by histopathological findings of LNB on POD 96 (Figure 3G). The drain was removed at POD 100. Sepsis occurred again on POD 101, and a wound was opened to remove a remnant of intra-abdominal abscess and to lavage the cavity directly. This direct approach was effective for infection control. Continuous hemodiafiltration was halted on POD 112, and he left the ICU on POD 120. The drain for ascites discharge was removed at POD 129. A biliary tube was clamped on POD 136, and was removed on POD 169. Histopathological LNB findings on POD 179 showed typical findings of chronic hepatitis C as A2 F2 (Figure 3H). Azan staining revealed fibrosis (Figure 4B), although no progression of fibrosis was observed. The patient developed muscle loss and mental instability because of the long ICU stay. He returned temporarily to his home on POD 188, and was then discharged from hospital on POD 223. HCV-RNA was decreased to 1.3 log IU/mL on POD 222. However, the induction of DAAs was regrettably delayed in our patient, although liver dysfunction and progressive fibrosis were observed. DAAs of ledipasvir and sofosbuvir (Harvoni, Gilead Sciences, Foster City, CA, USA) were administered after hospital discharge to obtain a SVR.

Discussion

High viral loads in the first three months after LT have been associated with the severity of recurrent hepatitis C [12], and the level of HCV-RNA at two weeks after LT is considered an important risk factor for FHC after LT [12]. From the viewpoint of hepatitis recurrence, several donor factors, especially donor graft steatosis and older donor age, have been associated with an earlier and more severe recurrence of hepatitis C [1,13]. Our case had no risk factors from the deceased donor.

To overcome the inevitable insufficiency of allograft size during adult living-donor LT, we intentionally establish PV pressure (PVP) under 15 mm Hg [14]. However, in this case, we did not perform PVP vigilance, because a deceased donor provided a whole liver allograft, and the actual graft volume was sufficient. From the viewpoint of recurrent hepatitis C, hepatic venous portal pressure gradients are good predictors of clinical decompensation due to recurrent hepatitis C [15]. The PVP value during LT might have been an informative predictor in our case, if PVP had been measured.
Corticosteroid usage has also been reported to have an important role in recurrent hepatitis C [16,17]. Treatment of both acute cellular rejection with multiple boluses of corticosteroids and rapid tapering of steroids have been linked to recurrent disease [16,17]. From a retrospective viewpoint, in this case, we performed SPT with rapid tapering, and thereafter, recurrent hepatitis C appeared to worsen. SPT was employed to control ARDS caused by sepsis, however, SPT might have triggered FCH.

Some DAAs should not be used in patients with Child C cirrhosis and/or severe renal impairment [4]. In our case, based on the results of genotype and resistance-associated variants, daclatasvir and asunaprevir were considered suitable treatments. Cirrhosis with a Child-Pugh score of B or C contraindicates the use of these drugs because of side effects. When there is a decision against using DAAs for FCH, allograft dysfunction may be severe if based on the Child-Pugh score.

**Figure 5.** Interventional radiology via percutaneous transhepatic approach. (A) Intraabdominal abscess compressed the venous graft, and therefore portal inflow continuously decreased. (B) The SMV and IMV flowed into the pancreaticoduodenal arcade and hepatoduodenal ligament. (C) Balloon dilatation (blue arrow) and stent placement (red arrow) were completed. Thereafter, the portal inflow was markedly improved. (D) The SMV and IMV flowed into the jumping venous graft and the portal flow was improved.
Child-Pugh score is useful to predict the outcome of surgery in cirrhotic patients, and to stratify patients on the waiting list for LT [18]. Then, a simple question arises. Even if serum ALT levels and the METAVIR system for histologic findings in chronic hepatitis C are used in transplanted allografts [19,20], is an assessment of the Child-Pugh score necessary even in allograft dysfunction after LT? In our case, the actual biochemical data were AST of 157 U/L, ALT of 311 U/L, GGT of 269 U/L, and T-Bil of 19.2 mg/dL. Even though the Child-Pugh scoring system is useful for assessing liver cirrhosis, it is not suitable for evaluating allograft dysfunction after LT. Retrospectively, we regret the delay in a decision to use DAA in this case. The last few years have seen an increase in the introduction of DAAAs [1,2]. Carefully considered DAA induction provides hope for the development of new protocols that are safer and more effective, even in post-transplant situations.

Diagnosis of FCH is made based on histopathological assessment, with biopsy [1,2,21]. Definitive diagnosis of FCH after LT is made upon the fulfillment of all of the following criteria [1,2,22]: 1) more than 1 month after LT; 2) serum level of T-Bil >6 mg/dL; 3) serum levels of alkaline phosphatase and GGT >5 times the upper limit of normal range; 4) the presence of characteristic histopathology on LNB (ballooning of hepatocytes, absence of inflammation, and cholangiocellular proliferation without bile duct loss); 5) very high serum levels of HCV-RNA; and 6) absence of surgical biliary complications and absence of evidence of hepatic artery thrombosis.

Although there was a combined impact of sepsis, portal flow decrease, and recurrent hepatitis C on graft failure in our case, it is interesting that histopathological findings of recurrent hepatitis C were consistently detectable from the first LNB. Although FCH is a rare variant of viral hepatitis, it should be emphasized that a prompt diagnosis is important for the management of adult recipients after LT [1,2,23,24]. Histopathological examination and HCV-RNA measurement should be performed in the event of unexplained laboratory findings and/or intractable ascites [1,2]. A real-time LNB is required, and histopathological findings should be carefully assessed for a precise diagnosis.

Conclusions

A real-time and precise diagnosis based on histopathological examination and viral measurement is indispensable for the adequate treatment of FCH. We conclude that well-considered DAA therapy should be aggressively introduced for FCH in LT recipients, and that they might improve the clinical course of potentially fatal FCH.

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Institutional review board statement

This report was approved by the institutional review board at Nagoya University Hospital.

Informed consent statement

The patient involved in this paper gave his written informed consent authorizing the use and disclosure of his protected health information.

Conflict-of-interest statement

All the authors have no conflicts of interest to disclose.

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