ABSTRACT

Fibrosing cholestatic hepatitis (FCH) is a life-threatening consequence of hepatitis C virus (HCV) infection occurring in a small minority of liver transplantation (LT) recipients. We herein report a case of early-onset FCH after living donor LT in a 47-year-old woman with HCV-related cirrhosis. The patient underwent balloon-occluded retrograde transvenous obliteration of a splenorenal shunt to treat an impaired portal flow on the sixth post-operative day (POD 6) and a bypass operation for hepatic artery thrombosis on POD 12. Thereafter, the serum bilirubin levels increased gradually; however, computed tomography revealed no evidence of biliary stricture. The serum HCV-RNA level on POD 27 was >7.8 log IU/mL. Histopathology of a needle graft biopsy performed on POD 28 revealed FCH with extensive portal fibrosis accompanied by mild inflammation, hepatocyte ballooning, and ductular proliferation with cholestasis. The patient received combination therapy with pegylated interferon, ribavirin, and double-filtration plasmapheresis for the treatment of early-onset FCH. Both the recipient and the donor carried the major genotype single nucleotide polymorphism (TT) at rs8099917 near the interleukin-28B gene. Furthermore, the HCV genotype was treatment-sensitive 2a. Nonetheless, the recipient died of hepatic failure on POD 211. Thus far, few cases of FCH occurring within 1 month after LT have been reported. In addition, the early onset of FCH may be an adverse prognostic factor.

HEPATITIS C VIRUS (HCV) infection is the most frequent indication for liver transplantation (LT) in Western countries and Japan [1]. Reinfection of the transplanted graft is a frequent complication that can lead to graft failure. The incidence of a sustained virological response (SVR) after LT is improved by the administration of combination therapy with pegylated interferon (PEG-IFN) and ribavirin (RBV). However, the incidence of postoperative HCV recurrence and related consequences remains high, and there is no general consensus on the optimal modality, timing, and dosing of antiviral treatment for post-LT HCV infection.

Fibrosing cholestatic hepatitis (FCH) is a severe consequence of HCV recurrence associated with early graft failure and an extremely poor prognosis. First described in the 1990s as a rare post-LT complication caused by recurrent hepatitis B virus infection [2], FCH is now recognized to be a significant risk factor for graft failure in HCV patients. However, to the best of our knowledge, few cases of FCH occurring within 1 month after LT have been reported. We herein report a case of FCH diagnosed on postoperative day 28 (POD 28) that eventually resulted in mortality.

CASE REPORT

A 47-year-old woman underwent living donor LT for treatment of chronic hepatitis C-related cirrhosis in January 2012. The
Child-Pugh and Model for End-Stage Liver Disease scores were 10 and 16, respectively. The pretransplantation HCV load and genotype were 4.9 log IU/mL and 2a, respectively. Other viral markers were negative. The donor was the patient’s husband, who had the matching A+ blood type. The grafted donor right lobe (685 g) was 59.5% of the recipient’s standard liver volume and had minimal steatosis (<1%) and no evidence of injury. The excised liver macroscopically appeared cirrhotic with mixed micronodules and macronodules. Histologically, well-developed fibrous septa contained dense mononuclear cell infiltrates and mild interface hepatitis.

Cyclosporine, methylprednisolone, and anti-CD25 antibodies (basiliximab) were administered for postoperative immunosuppression. On POD 6, Doppler ultrasound showed a decreased portal flow. Balloon-occluded retrograde transvenous obliteration (B-RTO), performed for occlusion of the splenorenal shunt, successfully increased the portal flow. On POD 12, no arterial flow was detected on Doppler ultrasound or computed tomography (CT), and emergency repeat laparotomy for hepatic artery reconstruction was performed. Arterial dissection extending from the common hepatic artery to the celiac artery associated with hepatic artery thrombosis (HAT) was detected. Angiembryogenesis due to dissection and thrombus formation was detected in the left accessory hepatic artery, which originated from the left gastric artery in this patient. Hepatic artery–abdominal aorta bypass through the retroperitoneum was performed using the right radial artery, resulting in an unobstructed hepatic artery blood flow, as detected on postoperative Doppler ultrasound.

Starting on POD 20, the serum bilirubin level began to gradually increase; however, CT showed no signs of biliary stricture. On POD 28, the bilirubin level reached 21.3 mg/dL, and we performed a liver biopsy. The biopsy showed extensive portal fibrosis with mild inflammation, delicate fibrous septa extending into the sinusoidal spaces, and ductular proliferation with cholestasis. Hepatocellular swelling and spotty acidophilic bodies were also present (Fig 1A). The serum HCV-RNA level was beyond the measurable limit (>7.8 log IU/mL). Based on these findings, the patient was diagnosed with FCH. Pegylated interferon α-2a (PEG-IFNα-2a) and double-filtration plasmapheresis (DFPP) were started immediately to decrease the viral load. We did not use RBV from the beginning due to the patient’s slight renal insufficiency. However, the results were unsatisfactory and we began the administration of combined PEG-IFNα-2b and RBV therapy on POD 46. A liver biopsy performed on POD 58 showed even greater portal fibrosis and continued ductular reactions with cholestasis; however, the earlier parenchymal degeneration and inflammation had improved (Fig 1B).

A liver biopsy performed on POD 155 to identify the cause of the patient’s liver dysfunction demonstrated extensive portal fibrosis with moderate lymphocyte infiltration, narrowing of the peripheral portal vein, and hepatocyte degeneration with acidophilic bodies around the periporal area. A liver biopsy performed on POD 169 showed moderate lymphocyte infiltration in the portal zone and centrilobular necrosis with hemorrhage and chronic inflammation (Fig 1C). The patient’s graft function gradually deteriorated, leading to hepatic failure. We considered registering the patient on the brain-dead donor LT list; however, we were unable to perform the procedure due to cytomegalovirus infection. Concurrent pneumonitis worsened the patient’s status, and she died on POD 211. A liver autopsy revealed shrinkage of hepatocytes with bridging fibrosis and blockage of the central hepatic vein (Fig 1D).

DISCUSSION

Hepatitis C recurrence after transplantation is almost universal, with HCV-induced graft hepatitis occurring in 80% of recipients and cirrhosis occurring in 30% of recipients within 5 years [3,4]. Combination therapy with PEG-IFN and RBV results in improved SVR rates. However, the SVR rate after LT is reported to be only 25% to 45% [5].

FCH, first described in the 1990s as a consequence of recurrent hepatitis B after LT [2], occurs in 1.8% of patients

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**Fig 1.** Histological findings of the liver biopsies performed on postoperative day (POD) 28 (A), POD 58 (B), and POD 169 (C) and a liver autopsy performed on POD 211 (D). (A) Hematoxylin-eosin (HE) staining showing a widened portal tract (HE staining ×100). (B) Extensive portal fibrosis was observed with continued ductular proliferation (HE staining ×100). (C) Centrilobular necrosis was observed with hemorrhage and chronic inflammation (HE staining ×200). (D) A liver autopsy revealing shrinkage of hepatocytes with bridging fibrosis and blockage of the central vein (HE staining ×40).
who undergo LT for HCV [6]. The liver histology of FCH is characterized by extensive portal fibrosis with immature fibrous bands extending into the sinusoidal spaces, hepatocyte ballooning, cholestasis, and mild to moderate inflammation. Recent studies have reported that an older donor age, extreme levels of viremia, and corticosteroid treatment for acute cellular rejection are significant risk factors for post-LT FCH [7–9]. In the present case, there was no clear evidence of acute cellular rejection, and the donor was relatively young (47 years); however, the serum HCV-RNA level was very high (>7.8 log IU/mL) as early as POD 10.

Hepatocytes under a high viral load may become apoptotic, thus leading to hepatocyte dropout despite the compensatory proliferative response of hepatocyte progenitors. The effects of viremia may be particularly severe in highly proliferative young progenitor cells [6]. The close proximity of these cells to biliary cells raises the possibility of cell–cell interactions that may disrupt bile acid transport, leading to cholestasis. Satapathy et al suggested that both the modest elevation in serum transaminases and the severe conjugated bilirubinemia observed in FCH are caused by decreased bile acid transport [6].

DFPP has been reported to be an effective prophylactic therapy against HCV recurrence [10]. In DFPP, the first filter separates plasma from blood, and then the plasma is passed through a fractionator with pores 10 to 40 nm in diameter to remove high-molecular-weight substances, including free HCV particles (55 to 65 nm in diameter). However, the effectiveness of DFPP for the prevention of recurrent hepatitis C after LT has been questioned [11]. Indeed, our patient showed a decreased viral load after receiving combined PEG-IFN + DFPP and PEG-IFN + RBV; however, an SVR was not obtained and the patient died within 7 months (Fig 2).

Immunosuppression has been implicated in the acceleration of recurrent HCV. Watashi et al reported that cyclosporine may have an inhibitory effect on HCV replication in vitro [12]. However, a retrospective analysis of data of 8809 chronic HCV liver transplant recipients obtained from the United Network for Organ Sharing did not find any beneficial effects of cyclosporine [13]. The efficacy of cyclosporine for preventing HCV recurrence warrants further clinical study.

The patient’s genotype may also influence the SVR during combined PEG-IFN and RBV treatment. Recently, a single nucleotide polymorphism (SNP) near the interleukin (IL)-28B gene on chromosome 19, rs8099917, was shown to be associated with the sensitivity to IFN and RBV combination therapy for chronic hepatitis C. A higher incidence of SVR has been demonstrated in patients carrying the major genotype (TT) compared with minor genotype carriers (TG or GG) [14]. IL-28B is a member of the IFN-λ family that triggers a type I IFN-like gene expression profile and has been shown to possess antiviral activity. Fukuhara et al investigated the correlation between IL-28B SNPs and the incidence of SVR in LT patients and found that the incidence of SVR was significantly lower when either the recipient or donor carried the minor genotype. Therefore, IL-28B genetic variations in both recipients and donors are significantly associated with the response to PEG-IFN and RBV therapy [15]. The TA dinucleotide repeat SNP, rs72258881, also located near the IL-28B gene, is positively associated with both the transcriptional activity of IL-28B and the therapeutic effects of combined PEG-IFN plus RBV [16]. In the present study, both the recipient and the
donor carried the major genotype at rs8099917 and both harbored 12 TA repeats at rs72258881. The HCV genotype was 2a, a viral genotype associated with a high response rate to PEG-IFN plus RBV [17]; therefore, the early-onset FCH and poor antiviral response shown by this patient were unexpected.

One of the criteria for the diagnosis of FCH is that it manifests more than 1 month after transplantation [1]. Although FCH can occur earlier in repeat-transplantation patients, it usually does not occur until 2 to 3 months after first transplantation [18]. Indeed, in the report by Satapathy et al, FCH was diagnosed on average 7.6 months after LT, and the first case was not observed until 3 months after LT [6]. In contrast, the patient described here was diagnosed with FCH within 1 month after undergoing LT. Although the reasons for this rare early-onset FCH are unclear, repeated invasive procedures (B-RTO on POD 6, bypass surgery on POD 12) may have contributed to the rapid deterioration of her clinical status. Further studies are required to determine the prognostic factors predictive of early-onset FCH and resistance to therapy in post-LT patients with HCV infection.

REFERENCES