Fibrosing cholestatic hepatitis in a kidney transplant recipient with hepatitis C virus

Takahiro Shinzato¹ · Taro Kubo¹ · Toshihiro Shimizu¹ · Koji Nanmoku¹ · Takashi Yagisawa¹

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Abstract

Fibrosing cholestatic hepatitis (FCH) is a fatal disorder that presents as a progressive deterioration of liver function over a period of several weeks to several months. It is caused by the direct cytotoxic effect of the over-expression of viral antigens on hepatocytes in immunosuppressed patients. Our patient was a 59-year-old man with hepatitis C virus (HCV) infection of genotype 2a who had suffered from end-stage renal disease due to diabetic nephropathy and underwent kidney transplantation. His serum total bilirubin levels gradually increased to 20 mg/dl and liver atrophy progressed during several weeks after kidney transplantation, which was initially difficult to distinguish from drug-induced liver injury. We diagnosed the condition as FCH on the basis of pathological findings and increased HCV viral load, and treated the patient with Glecaprevir/Pibrentasvir. However, the patient died of refractory hemorrhagic gastric ulcer and liver failure. Currently, it is possible to treat infections of all genotypes of HCV, even with end-stage renal disease, with direct acting antivirals. Furthermore, it is preferable to treat HCV before kidney transplantation considering the risk of FCH due to immunosuppressive therapy.

Keywords Fibrosing cholestatic hepatitis · Kidney transplantation · Hepatitis C

Introduction

Fibrosing cholestatic hepatitis (FCH) is a fatal disorder which manifests as a progressive deterioration of liver function for several weeks to several months [1–3] and is a result of the direct cytotoxic effects of over-expressed viral antigens on the hepatocytes of immunosuppressed individuals [1, 4–6]. The pathological features of FCH are periportal and perisinusoidal fibrosis, ballooning degeneration of the hepatocytes, marked cholestasis, ground glass appearance and minimal inflammation [2, 4, 7–9]. FCH was first reported in 1991 as a severe recurrence of hepatitis B in liver transplant recipients [1, 2] and has also been reported as a recurrence of hepatitis C in some kidney transplant recipients.

Herein we report the case of a kidney transplant recipient who developed FCH associated with hepatitis C virus (HCV). This is the first report of treating post-kidney

transplantation FCH with Glecaprevir/Pibrentasvir but was not successful.

Case report

We present the case of a 59-year-old man who underwent kidney transplantation in October 2017 and subsequently developed FCH. He was diagnosed with diabetes at the age of 50 and was diagnosed with hypertension and chronic hepatitis C at the same time. He developed nephrotic syndrome in 2015, and due to the gradually declining renal function, he started hemodialysis in January 2016. He visited our hospital for kidney transplantation in September 2016. Since his HCV genotype was 2a, he was offered the choice of preoperative interferon (IFN) therapy or post-operative Sofosbuvir/Ribavirin combination therapy. He selected the latter and underwent living kidney transplantation at our hospital on October 2017. The donor was his 54-year-old wife. Before transplantation, his serum was negative for hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, cytomegalovirus (CMV)-IgM and Epstein–Barr virus (EBV)-IgM, and it was positive for CMV-IgG and EBV-IgG. The

✉ Takahiro Shinzato
t.shinzato@jichi.ac.jp

¹ Department of Renal Surgery and Transplantation, Jichi Medical University Hospital, 3311-1 Yakushiji, Shimotsuke, Tochigi 3290498, Japan

total bilirubin was 0.43 mg/dl, aspartate aminotransferase (AST) 40 IU/l, alanine aminotransferase (ALT) 53 IU/l, gamma-glutamyl transferase (GGT) 250 IU/l and HCV viral load (by PCR) 3.9 LogIU/ml in the serum. Post-transplantation induction immunosuppressive therapy included tacrolimus, mycophenolate mofetil, methylprednisolone and basiliximab. The post-transplantation renal function was good, and the serum creatinine level decreased to 1.2 mg/dl. However, serum levels of AST, ALT and GGT began to rise on the fourth postoperative day. On the eighth postoperative day, the serum levels of AST, ALT, GGT, total bilirubin and HCV viral load were 134 IU/l, 213 IU/l, 432 IU/l, 0.86 mg/dl and 7.4 LogIU/ml, respectively, and he was discharged the following day. The levels of AST, ALT and GGT peaked on the 13th postoperative day at 209 IU/l, 297 IU/l and 577 IU/l, respectively, while the total bilirubin gradually increased thereafter. On the 35th postoperative day, the serum level of total bilirubin was 9.88 mg/dl and that of direct bilirubin was 7.70 mg/dl, and progressive atrophy of the liver was observed on computed tomography (Fig. 1). We replaced tacrolimus with cyclosporine, reduced the dose of mycophenolate mofetil and altered or stopped other drugs in light of the possibility of drug-induced hepatic injury. The patient's

total bilirubin and creatinine levels increased to 16.40 mg/dl and 1.7 mg/dl, respectively, on the 44th postoperative day, and he was re-hospitalized. A renal biopsy was performed on that day and showed non-specific changes. His total bilirubin levels increased thereafter to 20–25 mg/dl, prothrombin time began to be prolonged, and platelet count started declining. A liver biopsy was performed on the 50th postoperative day and showed remarkable canalicular cholestasis, hepatocyte ballooning, minimal inflammation, focal bile duct reactive changes, and fibrosis around hepatocytes (Fig. 2). These findings are not contradictory to FCH, but we could not negate the possibility of cholestatic dysfunction due to other causes such as drug-induced liver injury. We considered FCH because the patient's serum HCV viral load increased, and the hepatic signs did not improve even after changing or discontinuing the prescribed drugs. At this point, Glecaprevir/Pibrentasvir, which was not available in Japan when we had performed the kidney transplantation, was available. We started administering this drug on the 68th postoperative day. Although the HCV viral load decreased to 2.5 LogIU/ml, hemorrhagic gastric ulcers developed on the 72nd postoperative day. Endoscopic treatment was performed, but the disease was refractory, and as a result,

Fig. 1 Progression of liver atrophy (abdominal computed tomography). Pre-transplantation (a). 35th postoperative day (b). 61st postoperative day (c)

Fig. 2 **a** Hematoxylin and eosin stained sections at 100x magnification showing significant canalicular cholestasis, hepatocyte ballooning and minimal inflammation. **b** Silver-stained sections at 100x

magnification showing fibrosis around hepatocytes. **c** Cytokeratin 7 stained sections at 400x magnification showing focal bile duct reactive changes

hepatic failure progressed further. In addition, the patient developed cerebral infarction after the onset of atrial fibrillation on the 80th postoperative day and died on the 82nd postoperative day (Fig. 3).

Discussion

Several studies have reported that patients with FCH who had only reduced the immunosuppressant had poor prognosis [6, 10–13]. IFN treatment increased the risk of renal graft loss or decline of renal function due to rejection [11, 14], although in some cases treated with IFN rejection did not occur and sustained virological response (SVR) was achieved [15]. In contrast, treatment with direct acting antivirals (DAA) achieved SVR with good renal function [16, 17]. Hematopoietic stem cell transplantation has also resulted in good renal function with SVR [18]. In our case, although the viral load was decreased after DAA treatment, the patient unfortunately died. In previous reports, the duration between kidney transplantation to FCH onset

was 3 (0.3–120) (median (range)) months [6, 10–18]. In our case, the course of FCH was considerably faster and difficult to distinguish from drug-induced liver injury, thereby delaying the start of DAA treatment. It is necessary to take into account the possibility of the onset of FCH, as well as its rapid progression, when treating the patients with HCV with immunosuppressive drugs. In that event, it is important to perform a liver biopsy and start DAA treatment at the earliest.

At the time of kidney transplantation in this case, the antiviral therapy for HCV genotype 2a in cases with end-stage renal disease was only IFN therapy before kidney transplantation, and DAA was only available after kidney transplantation. After that, Glecaprevir/Pibrentasvir was released which can treat all genotypes of HCV in cases with end-stage renal disease before kidney transplantation. Considering the risk of FCH in patients with HCV following immunosuppressive therapy, it is preferable to treat HCV before kidney transplantation. Our report is the first so far on treating HCV-related FCH after kidney transplantation with Glecaprevir/Pibrentasvir. This is also the first

Fig. 3 Clinical course. *BXM* basiliximab, *GLE/PIB* glecaprevir/pibrentasvir, *mPSL* methyl-prednisolone, *PSL* prednisolone, *MMF* mycophenolate mofetil, *TAC* tacrolimus, *CyA* cyclosporine A, *PT*

prothrombin time, *GGT* gamma-glutamyl transferase, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *T-Bil* total bilirubin

time that HCV genotype 2a has been reported in HCV-related FCH after kidney transplantation, in contrast to previous reports of HCV genotypes 1, 3 and 4 [6, 10–18].

Liver biopsy was atypical but consistent with the features of FCH. The duration between kidney transplantation to liver biopsy was 1.5 months in our case, which in previous reports have been 11 (12–20) [median (range)] months. It is therefore possible that our pathological findings were a result of the relatively early biopsy. Although it was difficult to negate the possibility of other cholestatic disorders based on the histological findings alone, FCH was the most likely considering the clinical course and increase in viral load.

In conclusion, we described a case of severe HCV-related FCH after kidney transplantation, and recommend treating HCV before kidney transplantation.

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Compliance with ethical standards

Conflict of interest All the authors have declared no competing interest.

Human and animal rights This article does not contain any studies with human participants performed by any of the authors.

Informed consent Written informed consent obtained from the patient.

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