To the Editor,

Hepatitis C virus (HCV)-infected allogeneic hematopoietic stem cell transplantation (allo-HSCT) recipients have a higher incidence of liver cirrhosis over long-term follow-up compared to recipients without HCV infection [1, 2]. However, liver dysfunction related to HCV is usually mild in the first three months after allo-HSCT [2 3]. We present the development of progressive hepatic cirrhosis soon after allo-HSCT in HCV-infected recipient.
The clinical and histopathological features were very similar to fibrosing cholestatic hepatitis (FCH) caused by HCV reactivation. A fifty-year-old woman with myelodysplastic syndrome with excess blasts-1 was admitted to undergo allo-HSCT. The patient had a history of hepatitis C positivity (genotype 2a) for more than 20 years. Liver enzyme levels at admission were slightly elevated (aspartate aminotransferase 57 U/L, alanine aminotransferase 61 U/L, alkaline phosphatase 434 U/L, cholinesterase 115 U/L, total bilirubin (T-Bil) 1.2 mg/dL, and hepatitis C viral load 2.5×10^4 IU/mL). The serological tests for hepatitis B virus (HBV) and polymerase chain reaction for HBV-DNA were negative. Computed tomography (CT) demonstrated hepatosplenomegaly. Abdominal ultrasonography (US) showed the coarse hepatic echostructure over entire liver with dull edge, smooth surface and straight hepatic vein without ascites or any signs of portal hypertension. which was consistent with chronic hepatitis. Since there were no signs of portal hypertension or cirrhosis, the patient was diagnosed with chronic hepatitis. Liver biopsy was not performed because of thrombocytopenia.

Just before transplantation, any risk factors except for the mild hepatic dysfunction and age were not found, and the hematopoietic cell transplantation-comorbidity index (HCT-CI) was 1 and age-adjusted HCT-CI score was 2 [4, 5]. In the meanwhile, bone marrow examination revealed the active disease with 6.7% of myeloblasts. Considering the situation, the patient underwent peripheral blood stem cell transplantation from her human leukocyte antigen-identical sibling after myeloablative conditioning with cyclophosphamide (120 mg/kg) and total body irradiation (12 Gy). Considering drug-induced liver dysfunction, we avoided the use of busulfan. Cyclosporine and short-term methotrexate were used for graft-versus-host disease (GVHD) prophylaxis. After neutrophil engraftment, T-Bil elevated up to 8.3 mg/dl and hepatitis C viral load was noted to have increased to 4.0×10^6 IU/mL on day 36 after allo-HSCT. Methylprednisolone was started at 1 mg/kg/day on day 36 for acute GVHD, with gradual improvement in liver test results. We performed deliberate observation for the patient with weekly US and monthly CT after allo-HSCT, which revealed the progressive liver atrophy accompanied with ascites.

On day 82 after allo-HSCT, the patient once again became jaundiced and hepatitis C viral load increased over 6.9×10^7 IU/mL. Transjugular liver biopsy showed bridging and pericellular fibrosis with architectural distortion, prominent ballooning and spotty necrosis, consistent with early cirrhotic changes, and severe hepatocyte damage (Figure 1A-D). There was mild portal inflammation without histologic evidence of the small bile duct changes of GVHD. Moreover,
there was not sinusoidal obstruction. It was unlikely that the hepatopathy would be caused by cyclophosphamide, considering the timing of administration. From the pathological findings and the increased viral load, HCV reactivation was assumed to be the cause of liver dysfunction.

Direct-acting antiviral (DAA) therapy with ledipasvir (90 mg/day) and sofosbuvir (400 mg/day) was started on day 110 after allo-HSCT. Although the viral load decreased, the patient developed liver failure and died on day 126 after allo-HSCT (Supplementary Figure 1).

A few case reports have been reported on FCH caused by recurrence of HCV in recipients of liver transplantation [3 6], renal transplantation [4 7], and allo-HSCT [5 8]. The histopathological findings of FCH included periportal fibrosis, ballooning degeneration of hepatocytes, prominent cholestasis, and paucity of inflammation [5 8]. Although cholestasis was not prominent in our case, other pathological findings and clinical course were very similar to those of FCH. We speculated that this discrepancy may be due to the timing of liver biopsy, which was performed immediately after the re-elevation of T-bil and presumably in the early phase of FCH.

Regarding DAA therapy for HCV in allo-HSCT recipients, the best timing of administration is at least three to six months after allo-HSCT [6]. In this case, we planned to start DAA therapy after discontinuation of immunosuppressive therapy. However, we started DAA therapy on day 110 after allo-HSCT, considering the increase in viral HCV and pathology.

Generally, the initiation of DAA therapy is recommended at least three to six months after allo-HSCT in HCV-infected recipients, because of the rarity of fulminant hepatitis caused by HCV reactivation in this period and the overlapping toxic effects or potential drug-drug interactions of DAA with other agents [9]. In this case, we started DAA therapy based on the liver pathology and the increased HCV viral load. However, earlier intervention with DAA soon after the initiation of corticosteroid therapy should be considered, because it is a major risk factor for viral replication.

There were some limitations on our clinical practice. First, pre-transplant liver status was not fully evaluated. Elastography should be considered to accurate evaluation for the degree of fibrosis [10]. Second, reduced intensity conditioning should be considered to avoid the HCV-associated hepatopathy, although HCI-CI and age-adjusted HCT-CI score were relatively low. Last, as stated above, earlier diagnosis and intervention with DAA might contribute to good outcome.
In conclusion, progressive cirrhosis in an allo-HSCT recipient with chronic hepatitis C infection is presented. Despite the several limitations, this case may give an alert of HCV-associated progressive hepatopathy early after allo-HSCT. In conclusion, the possibility of HCV recurrence should be also considered as the cause of progressive hepatopathy early after allo-HSCT.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Author Contributions

SK, ND, and KO contributed to the clinical care of the patient. TH assessed the pathological findings. YT assessed the radiological findings and performed the liver biopsy. KO supervised the project. SK and ND wrote the manuscript.

References


Figure legends

Figure 1. (A-D) Photomicrographs of transjugular liver biopsy specimen on day 82 after transplantation, when the patient once again became jaundiced and hepatitis C viral load increased.

(A) There was extensive bridging and pericellular fibrosis with architectural distortion (Silver staining, low power field).

(B) There was severe damage to hepatocytes. Lymphoid infiltration of the portal region was scarce (Hematoxylin and Eosin staining, low power field).

(C) Ballooning degeneration of hepatocytes was evident (Hematoxylin and Eosin staining, high power field).

(D) The hepatocytes varied in size with oxyphilic and vacuolated cytoplasm. Scattered focal necrosis was evident (black arrow) (Hematoxylin and Eosin staining, high power field).

Supplementary Figure 1. Clinical course of the patient showing serial changes in her liver function. Abbreviations: DAA, direct-acting antiviral therapy; CyA, cyclosporine; mPSL, methylprednisolone; CY, cyclophosphamide; TBI total body irradiation; rPBSCT, peripheral blood stem cell transplantation from related donor; ALP, alkaline phosphatase; ALT, alanine aminotransferase; T-Bil; total bilirubin; HCV, hepatitis C virus.

* DAA included ledipasvir (90 mg/day) and sofosbuvir (400 mg/day).
† 1,000 mg of methylprednisolone was administered for 3 days.
ALT, ALP (U/L)

T-Bil (mg/dL)

Liver biopsy

HCV-RNA (IU/mL)

Days after transplant

CyA mPSL 60 mg/day 60 mg/day tapering

DAA*

Pulse therapy

ALP

ALT

T-Bil

CyA + TBI sMTX PBSCT

2.5 × 10^4 4.0 × 10^6 6.9 × 10^7

4.0 × 10^6 6.9 × 10^7 4.0 × 10^9

Supplementary Figure 1

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