In the 1980s, human immunodeficiency virus (HIV)- and hepatitis C virus (HCV)-contaminated blood products were administered to patients with hemophilia. Consequently, many patients developed chronic hepatitis, and some showed progression to liver cirrhosis requiring liver transplantation. Although the maintenance of hemostasis is indispensable and plays a key role in a successful operation, it is often difficult to achieve in patients with hemophilia (1,2). Despite continuous factor VIII/IX administration, catastrophic coagulopathy during transplantation can develop because of the co-existing severe thrombocytopenia requiring HLA-matched platelet products, which are difficult to obtain quickly. To maintain adequate platelet counts (> 5 × 10^9/µL) while awaiting liver transplantation, a thrombopoietin receptor agonist and rituximab were administered. During surgery, factor VIII concentrate was administered according to a previously planned protocol. Adequate hemostasis was obtained, and the operation was completed without uncontrollable coagulopathy. The postoperative course was uneventful, and the patient was discharged on postoperative day 41. Detailed planning is required for surgical patients with hemophilia and HIV/HCV cirrhosis, especially for those with a diverse spectrum of anti-HLA antibodies.

**SUMMARY:** We report the second case of deceased donor liver transplantation in a patient co-infected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) in Japan. A 48-year-old patient with hemophilia A was infected with HIV and HCV through contaminated factor VIII concentrate in his childhood and developed cirrhosis and hepatocellular carcinoma. The patient was on the transplant list for a deceased donor liver. The patient had broad spectrum anti-HLA class I and II antibodies, which may be attributed to repeated whole blood transfusions in the past. Catastrophic coagulopathy during the surgery was predicted because of the underlying hemophilic status and severe thrombocytopenia requiring HLA-matched platelet products, which are difficult to obtain quickly. To maintain adequate platelet counts (> 5 × 10^9/µL) while awaiting liver transplantation, a thrombopoietin receptor agonist and rituximab were administered. During surgery, factor VIII concentrate was administered according to a previously planned protocol. Adequate hemostasis was obtained, and the operation was completed without uncontrollable coagulopathy. The postoperative course was uneventful, and the patient was discharged on postoperative day 41. Detailed planning is required for surgical patients with hemophilia and HIV/HCV cirrhosis, especially for those with a diverse spectrum of anti-HLA antibodies.

In the 1980s, human immunodeficiency virus (HIV)- and hepatitis C virus (HCV)-contaminated blood products were administered to patients with hemophilia. Consequently, many patients developed chronic hepatitis, and some showed progression to liver cirrhosis requiring liver transplantation.

Although the maintenance of hemostasis is indispensable and plays a key role in a successful operation, it is often difficult to achieve in patients with hemophilia (1,2). Despite continuous factor VIII/IX administration, catastrophic coagulopathy during transplantation can develop because of the co-existing severe thrombocytopenia due to underlying liver cirrhosis. Administration of factor VIII/IX concentrates and platelet transfusions are the only treatment options in this situation. However, before factor VIII/IX concentrates became available, repeated fresh whole blood transfusions were given to patients with hemophilia, and these patients were sometimes highly sensitized and developed diverse anti-HLA antibodies. The presence of anti-platelet antibodies made random platelet transfusions ineffective and coagulopathy difficult to control.

Previous whole blood transfusions in patients with hemophilia also caused some of the anti-HLA class II antibodies to act as preformed donor-specific antibodies (DSA) and negatively affect graft survival (3). Consequently, special precautions are required for liver transplantation candidates with hemophilia and cirrhosis, and a multidisciplinary approach should be considered.

Here, we report a case of deceased donor liver transplantation (DDLT) in a hemophilia A patient co-infected with HIV and HCV, in whom anti-platelet antibodies and broad spectrum DSA were both present.

The patient was a 48-year-old man with hemophilia A who had been treated with repeated whole blood transfusions in his childhood. After the factor VIII concentrate became available, he had been treated with this product. However, the product was found to be contaminated with HIV and HCV. When the patient was 22 years old, he was found to be infected with HIV through routine infection screening after a blood transfusion. Sixteen years later, serological screening for HCV was performed, and the result was positive. Antiviral therapy for HCV was initiated, but he could...
not tolerate the interferon-based therapy due to severe anemia. Seven years after his HCV infection diagnosis, hepatocellular carcinoma (HCC) developed, and radiofrequency ablation (RFA) was performed. Cirrhosis progressed thereafter, and the patient was added to the transplant list for a DDLT, with model of end-stage liver disease (MELD) score of 14 (Table 1). For HIV infection, the patient received antiretroviral therapy (ART), and the HIV-RNA level was below the level of detection when the patient was placed in the transplant list. Although there was a recurrence of HCC, the tumor burden was controlled within the Milan criteria by RFA and transcatheter arterial chemoembolization throughout the course of treatment. While awaiting a liver transplantation, the patient received random platelet transfusions due to a platelet level of 2.7 ×

| Listing day | Operation day | Discharge day |
|------------|--------------|--------------|
| Leukocyte count (/µL) | 3300 | 3100 | 2400 |
| Hemoglobin (g/dL) | 11.6 | 8.5 | 10.1 |
| Hematocrit (%) | 34.7 | 26.9 | 31.1 |
| Platelet count (x 10^4/µL) | 5.3 | 9.8 | 5.9 |
| Prothrombin time (%) | 43.6 | 37.1 | 82.8 |
| PT-INR | 1.58 | 1.71 | 1.10 |
| APTT (sec) | 105.7 | 61.4 | 40.1 |
| Total Protein (g/dL) | 7.0 | 5.8 | 6.3 |
| Albumin (g/dL) | 2.3 | 2.7 | 4.0 |
| Total Bilirubin (mg/dL) | 2.8 | 2.6 | 0.6 |
| Direct Bilirubin (mg/dL) | 0.6 | 0.5 | 0.1 |
| AST (U/L) | 70 | 33 | 34 |
| ALT (U/L) | 37 | 19 | 35 |
| γGTP (U/L) | 21 | 11 | 29 |
| Urea nitrogen (mg/dL) | 8 | 10 | 16 |
| Creatinine (mg/dL) | 0.60 | 0.81 | 0.78 |
| Sodium (mEq/L) | 139 | 139 | 140 |
| Potassium (mEq/L) | 4.0 | 3.7 | 4.9 |
| Chloride (mEq/L) | 111 | 108 | 109 |
| AFP (ng/mL) | 8.5 | 6.6 | 2.0 |
| PIVKA II (mAU/mL) | 32 | 11 | 18 |

Fig. 1. Correlation between platelet level and TPO receptor agonist (romiplostim) dose, and DSA Mean fluorescence intensity level during pre- and perioperative period.
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10^4/µL, but his platelet count was not elevated by the transfusions. A screening study for anti-HLA antibodies revealed a diverse array of HLA type I and II antigens. These results suggested that only HLA-matched platelet transfusions were suitable for treatment. However, HLA-matched platelets are not always available. Therefore, proceeding with the liver transplantation procedure without appropriate platelet products carried a potential risk, since it was expected that severe coagulopathy could develop during transplantation. A strategy was formulated to use the thrombopoietin receptor agonist, romiplostim, to achieve an adequate platelet level preoperatively. The local institutional review board of Hokkaido University granted permission for compassionate use of romiplostim (015–0010).

Romiplostim injections were started at a weekly dose of 75 µg (1 µg/kg). Our target platelet count level was 5–10 × 10^4/µL, and the romiplostim dose was adjusted according to the platelet count. Biweekly ultrasounds were performed to monitor portal vein thrombosis, a major complication of romiplostim use. Romiplostim had been administered for 1 year and 8 months, and no side effects, including portal vein thrombosis, were observed throughout the course. The correlation between platelet counts and romiplostim dose is shown in Fig. 1.

Rituximab at 50 mg/m^2 was administered soon after the patient was listed for transplantation, with the expectation of reductions in anti-HLA class I and II antibody levels.

After 1 year and 8 months of being on the transplant list, a suitable cadaveric donor became available, and liver transplantation was carried out. The patient’s platelet level was 7.0 × 10^4/µL just before the transplantation surgery. Due to the presence of preformed DSA, plasmapheresis was performed twice before transplantation. As planned, a 5,000 U factor VIII concentrate bolus was administered before incision, and a continuous dose of 300 U/h of factor VIII concentrate was initiated. Continuous administration of factor VIII concentrate was tailored based on blood loss, aiming at a factor VIII level of at least 80% (Fig. 2). Coagulopathy did not develop during surgery, and complete hemostasis was achieved. The estimated blood loss was 7,140 mL. Additional plasmapheresis was performed, and rituximab 50 mg/m^2 was administered after the surgery. DSA levels rapidly decreased due to these treatments (Fig. 1). Administration of supplemental factor VIII concentrates was discontinued on postoperative day 12. Graft function recovered appropriately, and anti-HIV therapy (emtricitabine/tenofovir disoproxil fumarate, and raltegravir) was resumed on postoperative day 10. The postoperative course was uneventful, and the patient was discharged on postoperative day 41.

Twelve weeks after the transplantation, genotype IV HCV infection was treated with sofosbuvir and daclatasvir, and a sustained viral response was achieved. Three years after the liver transplantation, the patient is free from hemophilia treatment and is currently in good health without the recurrence of HCV infection or HCC.

In this case, maintenance of hemostasis was a challenging problem. Strategies to achieve complete hemostasis in hemophilia patients using continuous factor VIII administration have been reported (2), but an additional strategy was needed for our patient due to...
the presence of anti-platelet antibodies. While the only solution used to be HLA-matched platelet transfusion, which was not always available, romiplostim, a thrombopoietin (TPO) receptor agonist (4), has become a treatment option for cirrhosis patients with anti-platelet antibodies. Romiplostim directly stimulates megakaryocytes and increases the platelet count. Romiplostim has previously been used for idiopathic thrombocytopenic purpura and myelodysplastic syndromes (5). Recently, TPO receptor agonists have been used effectively in patients with liver cirrhosis (6–8), and short-term use in candidates for liver transplantation has also been reported (9).

Our patient underwent long-term treatment while waiting for a DDLT. Platelet counts were evaluated weekly, and the dose was accordingly managed to prevent platelet counts from exceeding 20 × 10⁴/µL. As the platelet count was maintained under 20 × 10⁴/µL, portal vein thrombosis did not occur for 1 year and 8 months. This case illustrates the safe preoperative use of romiplostim with close monitoring.

It was estimated that over 800 hemophilia patients were infected with HIV/HCV in Japan, and the number of liver transplantation candidates with anti-platelet antibodies and/or broad spectrum preformed DSA may increase in the future. Careful preoperative planning is required for these patients.

**Acknowledgments** The authors were supported by a Grant-in-Aid for Research on HIV/AIDS from the Ministry of Health, Labour, and Welfare of Japan, the “Eguchi project”. The authors thank the members of the research group on HIV/AIDS from the Ministry of Health, Labour, and Welfare of Japan, the “Eguchi project” for their continuous support.

**Conflict of interest** None to declare.

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