LETTER TO THE EDITOR

Orthotopic liver transplantation for liver cirrhosis due to hepatitis C virus in patients with hemophilia A: two benefits of one procedure

Introduction Patients with hemophilia who were treated with clotting factor concentrates from nonsterilized pooled plasma until the mid-1980s have been infected with hepatitis C virus (HCV) in almost 100% of the cases worldwide before the health risk had been recognized.[1,2] At that time, replacement treatment of hemophilia in Poland was based on fresh frozen plasma, cryoprecipitate, and blood transfusion; therefore, our patients avoided infection with human immunodeficiency virus, but as many as 95% of the individuals with severe hemophilia became anti-HCV positive owing to infusions of blood products that had not been inactivated with any of the known antiviral methods.[3] This situation continued until 1992 when routine testing for HCV was introduced. Hemophilia patients born after 1991 have been rarely infected with blood-borne viruses.[3]

The appropriate management of hemophilia improved life expectancy in this disease giving enough time for the development of HCV-related end-stage liver disease (ESLD) such as decompensated cirrhosis and hepatocellular carcinoma (HCC). Approximately 30% of HCV-infected patients develop cirrhosis within 20 to 30 years of infection, and, consequently, a significant proportion of hemophiliacs become candidates for liver transplantation (LT), which is the treatment of choice for HCV-related ESLD. Initially, there were some concerns regarding this operation in patients with hemophilia, but there is a growing evidence that survival after LT in patients with hemophilia is acceptable and comparable to that of HCV-positive patients without clotting factor deficiencies. Excessive clotting factor replacement in the perioperative period is rarely necessary, and, additionally, a given hemostatic defect can be completely cured in the majority of the patients as both factors VIII (FVIII) and IX are synthesized by the transplanted liver. These observations raise questions of whether LT is a good treatment for hemophilia itself. Currently, the only recommendation for LT in this setting is ESLD (most commonly caused by chronic viral hepatitis). The arguments for this approach include morbidity and mortality related to LT, long-lasting immunosuppression with numerous side-effects, and potentially aggressive recurrence of HCV infection after LT.

The present paper reports 2 cases of successful LT performed in one of the Polish transplant centers for patients with severe and moderate hemophilia.

Patients and methods Two male patients with hemophilia A underwent LT. A circulating anticoagulant (inhibitor) was not observed in any of the patients. The severity of hemophilia was determined on the basis of FVIII levels; the first patient had moderate hemophilia with an FVIII activity of 4%, and the second had severe hemophilia with an FVIII activity of less than 1%. An indication for LT was the end stage of chronic HCV genotype 1b infection acquired before 1991 through fresh frozen plasma and cryoprecipitate infusions that were neither sterilized nor tested for HCV. Before surgery, both patients were consulted by a hematologist. Coagulation parameters such as prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT), fibrinogen, factors V, VIII, and IX, as well as platelet count were measured. FVIII deficiency was supplemented using the following formula:

$$\frac{(100 - \text{baseline value}) \times \text{body weight (kg)}}{2}$$

to achieve from 80% to 100% of the normal concentration directly prior to LT. The FVIII level was measured perioperatively every 6 h and deficiency was corrected if needed. Coagulation was also monitored at the same time intervals by measuring PT, INR, and aPTT. A total hepatectomy and disease-donor LT using the piggyback technique were performed. The operative time was 7.5 h in both cases, and intensive care after LT was not necessary.

Case 1 A 52-year-old patient with moderate hemophilia A was scheduled for LT owing to decompensated liver cirrhosis type C and HCC. The main symptoms of ESLD were related to the signs of portal hypertension. The patient had a history of recurrent variceal bleeding and numerous binding ligations prior to LT. However, the synthetic function of the liver was fairly well preserved (Model of End-Stage Liver Disease [MELD] score, 9; Child–Pugh score, A5; bilirubin level, 0.8 mg/dl; INR, 1.2; PT, 15 s; aPTT, 41 s; albumin level, 3.9 g/dl). The patient was treated with interferon and ribavirin twice in the past. He responded to a 24-week treatment with recombinant interferon and ribavirin, but relapsed soon after stopping the therapy and did not respond to a treatment with pegylated interferon and ribavirin. The second treatment was introduced in the cirrhotic phase of HCV infection confirmed by liver biopsy.

LT that required FVIII replacement was performed in December 2007. There were no complications either intra- or postoperatively. FVIII was monitored and deficiency corrected. Intraoperative bleeding was not significant and similar to that observed in patients without hemophilia. The patient did not require either packed red blood cell or platelet transfusion; he received 13 units of fresh frozen plasma during LT. FVIII was only substituted until the second day after the surgery, and its concentration was 87% at discharge 15 days later. During follow-up, FVIII levels varied from 53% to 84% and no bleeding was observed. Invasive procedures (liver biopsy, thyreoidectomy) performed after LT did not require correction of any coagulation parameter. He was successfully treated with pegylated interferon and ribavirin administered for 48 weeks 3 years after transplantation. Currently, the patient is free of hemophilia and HCV infection.

Case 2 A 45-year-old patient with severe hemophilia was scheduled for LT owing to decompensated cirrhosis type C. Synthetic liver function was significantly compromised (MELD score, 15, Child–Pugh score, C10; bilirubin, 1.51 mg/dl; PT, 20 s; aPTT, 101 s; INR, 1.8; albumin level, 2.45 g/dl). We also observed signs of portal hypertension (refractory ascites and recurrent variceal bleeding). Antiviral treatment with pegylated interferon and ribavirin was administered once before LT but was terminated owing to lack of response.

The patient was transplanted in January 2014. There were no complications either during or after LT. FVIII and other coagulation parameters were monitored and deficiencies corrected. Intraoperative bleeding was not significant, and it was similar to that observed in patients without hemophilia. The patient received 4 units of packed red blood cells and 5 units of fresh frozen plasma during LT. FVIII was substituted during the surgery and only once after the surgery (2000 IU), following which normal levels were achieved and maintained. At discharge (13 days later), the FVIII activity was 133% of the normal range. During follow-up, the value varied between 58% and 89%. No new symptoms of hemophilia are currently observed. Liver function tests are still normal but the patient is monitored for the expected recurrence of HCV infection.

Discussion Considering the epidemiology of HCV infection among hemophiliacs born before 1991 and the natural history of HCV-related liver disease, a substantial number of referrals to the transplant centers owing to hemophilia and HCV-related ESLD should be observed in Poland. However, the number is surprisingly low despite the fact that approximately 1000 patients with severe hemophilia have chronic C hepatitis.[4] One of the possible explanations is that treating physicians do not consider LT to be beneficial in patients with hemophilia and are reluctant to refer them to transplant surgeons. Another possibility is a shorter lifespan in Polish hemophiliacs treated before the era of recombinant or lyophilized factor concentrates and, consequently, patients with hemophilia and ESLD are in a considerable minority today. The aim of our paper was to show that LT in patients with severe and moderate hemophilia is a feasible procedure, which does not only cures cirrhosis and HCC but can also lead to permanent correction of clotting factor synthesis.[2,5] Successful anti-HCV treatment after LT (in the absence of advanced fibrosis) is also feasible, and both strategies can help patients with hemophilia avoid 2 major medical threats.

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Conflict of interest The authors declare no conflict of interest.

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