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Peculiarities of orthotopic liver transplantation in patients with liver cirrhosis and severe hemophilia A

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Abstract

In the presented clinical case reports, patients with decompensated liver cirrhosis resulted from chronic viral hepatitis C, being stable responders to antiviral therapy and having severe hemophilia A, underwent orthotopic liver transplantation from a post-mortem donor. The volume of intraoperative blood loss and the course of the immediate postoperative period on the background of the replacement therapy with recombinant VIII coagulation factors did not differ from other liver transplant recipients of the City Clinical Hospital n.a. S.P. Botkin. In the late postoperative period, the level of coagulation factor VIII returned to normal in patients, which made it possible to cancel the replacement therapy.

Keywords: liver cirrhosis, hemophilia A, orthotopic liver transplantation

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CVH C, chronic viral hepatitis C

FVIII, blood coagulation factor VIII

Introduction

Hemophilia A is a genetic hereditary recessive X-linked blood clotting disorder caused by a deficiency of antihemophilic globulin, blood clotting factor VIII (FVIII) [1], which is synthesized by kidney, spleen, macrophages, and bone marrow cells; however, endothelial cells of the peribiliary vascular plexuses of the liver are the main source of circulating FVIII [2, 3]. The literature distinguishes "hepatic" and "extrahepatic" pool of factor VIII [2], the normal concentration of the factor is 50–100%. Until the mid-1980s, therapy in patients with hemophilia consisted of the transfusion of blood components, which in some cases led to infection with hepatitis B and C viruses, followed by the development of end-stage liver diseases [4]. Patients with hemophilia infected with HCV have a higher risk of developing end-stage liver disease with a risk of decompensation of 1.7% at 10 years and 10.8% at 20 years [5]. The only definitive treatment for liver cirrhosis is transplantation [6, 7], and although the presence of a coagulation disorder may negatively affect the course of the early and late postoperative period after liver transplantation, the absence of a genetic defect in an organ donor may have a positive effect on the course of hemophilia.

Clinical Case Reports

Patient F., born in 1969, was diagnosed with hemophilia A, severe form (FVIII lower than 1%) in the maternity hospital. Subsequently, in connection with recurrent bleeding, hemarthrosis, and anemia, the transfusions of blood components were performed 1–2 times a month. Since 2004, a replacement therapy with FVIII drugs at a dose of 2000 IU every other day has been performed. Anti-HCV antibodies were first identified in 1999. In 2005, an antiviral therapy with pegylated interferon, 1 million IU every other day, was given for 5 months, interrupted due to severe thrombocytopenia occurred before a virological response was achieved. From 2005 to 2006, the patient was hospitalized 23 times for exacerbation of hemorrhagic syndrome: 2 times for hemarthrosis of the right ankle joint, 3 times for hemarthrosis of the right elbow joint, 3 times for hemarthrosis of the right knee joint, once for epistaxis, 3 times for hemarthrosis of the right hip joint, 4 times for hemarthrosis of the left ankle joint, 3 times for macrohematuria, 2 times for hemarthrosis of the right shoulder joint, 2 times for bleeding from the gums.

In 2006, esophageal varices were diagnosed for the first time. In 2007, liver elastography diagnosed F4 fibrosis assessed by METAVIR. In 2007 and 2009, repeated courses of antiviral therapy with pegylated interferon-α-2a were undertaken. In 2010, the endoscopic ligation of the esophageal veins was performed. Courses of the direct antiviral therapy were given in 2011-2013, and a virological response was achieved. In 2015, the patient underwent Patsiora surgery for bleeding from gastric venous varices; later, in 2016-2017, endoscopic ligation of esophageal veins was performed for recurrence of esophageal venous varices.

In June 2021, the patient referred to the City Clinical Hospital n.a. S.P. Botkin to address the issue of liver transplantation. He was

diagnosed with Child-Pugh-Turcotte Class B liver cirrhosis resulted from chronic viral hepatitis *C* (CVH *C*), MELD 12; portal hypertension; venous varices of the esophagus, stage 3. The examination revealed no contraindications to surgical treatment; he was included in the waiting list for liver transplantation. In July 2021, a planned endoscopic ligation was performed for grade 3 esophageal varices. On February 1, 2022, orthotopic cadaveric liver transplantation was performed. In the perioperative period, the following replacement therapy was administered: FVIII 4000 IU, followed by FVIII 2000 IU daily.

Intraoperative blood loss was 800 mL. The postoperative course was uneventful. He was discharged from hospital on the 8th postoperative day. Immunosuppressive therapy with extended release calcineurin inhibitor in monotherapy regimen was given. Last administration of FVIII took place in in March 2023 Further, within the follow-up dynamic measurements, the FVIII level returned to normal; and for 18 months of follow-up it was at the level of 50%.

Patient B., born in 1973, was diagnosed with a severe form of hemophilia A (FVIII less than 1%) in childhood, for which the transfusion of blood components was repeatedly performed. Further he was on FVIII replacement therapy with a monthly requirement of 45,000 IU. Chronic viral hepatitis C was first diagnosed in 1989, no antiviral therapy was given. In 2018, he was diagnosed with liver cirrhosis, and portal hypertension. In 2019, he was repeatedly admitted at various hospitals for recurrent bleeding from esophageal venous varices. In 2020, he underwent antiviral therapy with daclatasvir and sofosbuvir with achieving a sustained virological response. In 2019, for the first time, he was hospitalized to the City Clinical Hospital n.a. S.P. Botkin with symptoms of liver cirrhosis decompensation. The following diagnosis was made: Child-Pugh-Turcotte Class B liver cirrhosis resulted from

CVH C, MELD 17; portal hypertension; stage 2 esophageal varices; splenomegaly, hypersplenism, thrombocytopenia ($45x10^9$/L); hepatocellular insufficiency (hypoprothrombinemia, hypoalbuminemia, mild parenchymal jaundice); West-Haven Grade 1 hepatic encephalopathy; severe form of hemophilia A. While on conservative therapy, positive dynamics was achieved; the patient was examined and included in the waiting list for cadaveric liver transplantation. Due to a high risk of bleeding, the transjugular intrahepatic porto-systemic shunting and simultaneous embolization of the splenic artery were indicated (Fig. 1).

In September 2021, the TIPS placement was undertaken (Fig. 1).

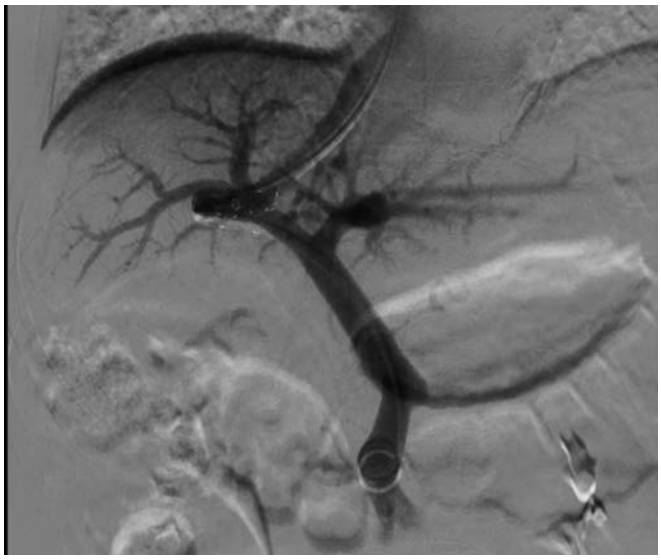

Fig. 1. Portogram, TIPS placement. Intrahepatic anastomosis between the portal vein system and the right hepatic vein has been formed

TIPS transjugular intrahepatic portosystemic shunt

At 3 months after the intervention, abdominal CT revealed a portosystemic shunt in a typical location, signs of impaired blood supply to the spleen (Fig. 2). Clinically, 2 weeks after the intervention, the

platelet level increased to $80x10^9$/L, followed by its normalization after 6 weeks ($167x10^9$/L).

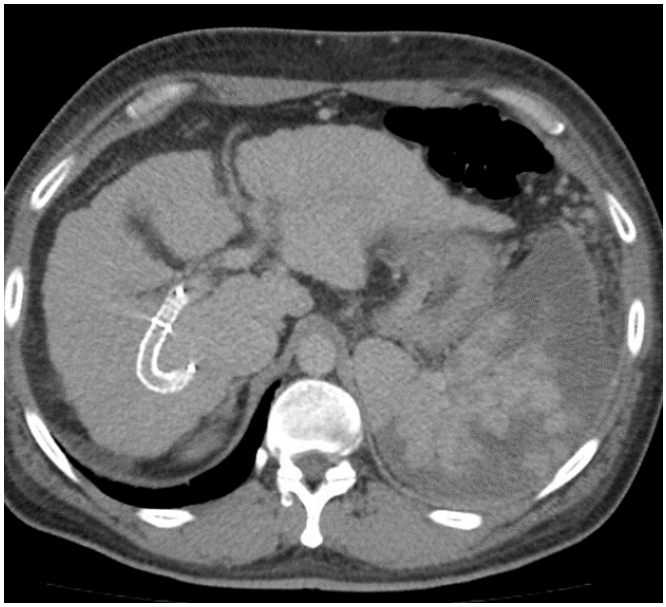

Fig. 2. Multislice spiral computed tomography of the abdominal organs with intravenous contrast. Portosystemic shunt in a typical location. Postoperative abnormalities in the spleen

In April 2022, orthotopic transplantation was performed. The following scheme of replacement therapy was used: the administration of FVIII concentrate 8000 IU, followed by FVIII 2000 IU daily.

Intraoperative blood loss was 1200 mL. The early postoperative period was uneventful. The patient was discharged on the 10th postoperative day. Immunosuppressive therapy with an extended release calcineurin inhibitor in a monotherapy regime was conducted. Further, within the dynamic follow-up measurements, the level of factor VIII returned to normal and at the moment of writing the article was at the level of 60%.

Discussion

The development of replacement therapy with recombinant factor has revolutionized the treatment for hemophilia. Currently, surgical interventions of varying duration and complexity in patients with hemophilia are not associated with a high risk of hemorrhagic complications. We presented the clinical case reports where the patients underwent repeated minimally invasive and open surgical interventions that were not accompanied by intraoperative bleeding. However, given that the progression of liver cirrhosis inevitably leads to the coagulopathy and thrombocytopenia aggravation, the risk of hemorrhagic complications in these patients was extremely high.

The only definitive treatment for these patients is orthotopic liver transplantation. In the world literature today there are no recommendations for the management of recipients with hemophilia in the perioperative period, however, there are publications confirming the advisability of transplantation in these patients. In a study by S. Yokoyama et al. (2011), the recipients with hemophilia A and liver cirrhosis resulted from CVH C without HIV coinfection had long-term results comparable with the general population of liver recipients [8]. According to the authors, in all patients, the levels of clotting factors increased to normal values as soon as at 72 hours after surgery, and none of the recipients needed replacement therapy anymore. Similarly, in a series of clinical cases studied by C. Alonso Madrigal and et al. (2018), three patients with hemophilia A and a patient with type 3 von Willebrand disease required no replacement therapy after liver transplantation [9]. An observational study by M.V. Ragni et al. (2018), as other studies of the above-mentioned authors, showed that against the background of modern replacement therapy with recombinant coagulation factors, the presence of hemophilia does not significantly affect the liver

transplantation outcome. Post-transplant survival was significantly lower only in the group of HIV-infected recipients with hemophilia, but it did not differ from long-term survival in HIV-infected patients without hemophilia [10].

Thus, based on the literature data and the clinical cases of using replacement therapy with factor VIII drugs we have presented here, orthotopic liver transplantation in these patients not associated with additional technical difficulties and does not lead to an increase in intraoperative blood loss and postoperative complications. An important feature of the postoperative course was the normalization of the level of coagulation factor VIII and the absence of the need for replacement therapy.

Conclusion

With the development of liver cirrhosis in patients with hemophilia A, orthotopic liver transplantation is not associated with additional risks of bleeding when using FVIII drugs. In addition to the correction of portal hypertension and the resolution of liver failure symptoms, it is possible to restore the blood concentration of antihemophilic globulin, followed by rejecting further replacement therapy.

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