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BRIEF REPORT

Z. Kadry
P. de Moerloose
E. Giostra
P. Morel
O. Huber
E. Meili
H. E. Blum
G. Mentha

Orthotopic liver transplantation in hemophilia B: a case report

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Z. Kadry · P. Morel · O. Huber · G. Mentha (✉)
Transplant Unit, Department of Surgery, University Hospital, CH-1211 Geneva 14, Switzerland

P. de Moerloose
Hemostasis Unit, University Hospital, CH-1211 Geneva 14, Switzerland

E. Giostra
Division of Gastroenterology, University Hospital, CH-1211 Geneva 14, Switzerland

E. Meili
Hemostasis Unit, University Hospital, Zurich, Switzerland

H. E. Blum
Medical Clinic B, University Hospital, Zurich, Switzerland

Abstract Liver transplantation is a treatment modality that is being used with increasing frequency in cases of liver-based metabolic defects. This is a case report of a patient with hemophilia B who was treated since childhood with factor IX replacement for recurrent hemarthroses. Subsequent hepatitis B (HBV) and C (HCV) infection had resulted in the development of chronic active hepatitis, ultimately leading to cirrhosis. Orthotopic liver transplantation performed for end-stage liver disease resulted in a rise in factor IX levels from 2 % to 83 % of normal values within 24 h postoperatively, and levels remained above 90 % of normal values after postoperative day 3 without factor IX replacement. To our knowledge, only two cases of hemophilia B treated by orthotopic liver transplantation have been reported. This procedure has, however, only been implemented in cases of terminal liver insufficiency in hemophiliacs.

Key words Hemophilia B, liver transplantation · Liver transplantation, hemophilia B

Introduction

The indications for hepatic transplantation have broadened considerably as the results of this procedure have continued to improve. It has been used to treat a wide variety of liver-based metabolic defects including hemophilia A and B [2, 4, 12, 15, 16, 18, 20].

Replacement of factors VIII and IX with pooled products in the past has placed hemophiliacs at a high risk of contracting hepatitis and HIV infection [1, 3, 5–9, 14, 19, 21, 22, 24]. Orthotopic liver transplantation has been used to correct the coagulation factor deficiency of hemophilia only in situations of concomitant liver failure [2, 12, 15, 16, 18, 20]. To our knowledge, only two patients suffering from hemophilia B have ever been treated by liver transplantation, both in North America [4, 15]. This is a report of the first patient in Europe in whom an underlying hemophilia B was successfully treated by orthotopic liver transplantation for end-stage liver insufficiency caused by hepatitis B (HBV) and hepatitis C (HCV) infection through past factor IX infusions.

Case report

P. W. is a 45-year-old patient diagnosed with hemophilia B of moderate severity since childhood, his mean factor IX levels measuring approximately 2 % of normal values. Multiple factor IX concen-

trate transfusions administered for recurrent hemarthroses resulted in chronic HBV and HCV infection, ultimately leading to a progressive deterioration in liver function. Two separate courses of alpha interferon therapy were administered in 1988 and 1992 for a duration of 6 and 3 months, respectively. At the end of each alpha interferon course, there was normalization of transaminase levels with disappearance of serum HBV replication indices, HBV DNA as well as HBeAg. In November 1993, however, P.W. developed an acute deterioration in his clinical status with the appearance of a progressively worsening jaundice, asthenia, refractory ascites, and mild-to-moderate hepatic encephalopathy. The reappearance of serum HBV DNA in December 1993 precipitated an unsuccessful attempt at treatment with intravenous famcyclovir. The latter was discontinued shortly after it was started due to the development of a generalized maculopapular rash attributed to an allergy to famcyclovir. Recurrent gastrointestinal hemorrhage secondary to severe portal hypertension necessitated prophylactic transfusions of factor IX concentrate and fresh frozen plasma three times a week.

In March 1994, a complete liver transplantation evaluation was undertaken. Serologic testing for HIV was negative. In April 1994, a compatible donor was identified and P.W. underwent hepatic transplantation. During the procedure, a total of 16 units of packed red blood cells, 22 units of fresh frozen plasma, and 10,800 units of factor IX concentrate were required.

Due to the continued presence of HBV replication preoperatively, as reflected by serum HBV DNA levels of 563 pg/ml, prophylactic antiviral therapy consisting of fresh frozen plasma rich in anti-hepatitis B immunoglobin and twice daily intravenous ganciclovir infusions of 5 mg/kg were administered for the first 2 postoperative weeks. Factor IX levels reached 83 % of normal values within the first 24 h and later remained at 90 %–100 % of normal levels without factor IX replacement.

P.W. is presently 1 year post-transplantation. He has resumed full-time employment. His coagulation factors continue to remain within the normal range (partial thromboplastin time 27.8 s, prothrombin time 85 %). He currently receives prophylactic ganciclovir therapy (5 mg/kg) three times a week, in addition to fresh frozen plasma rich in antihepatitis B immunoglobulin, in order to maintain anti-HBV surface antibody levels above 500 units/l. A follow-up liver biopsy performed in September 1994 showed no evidence of viral recurrence, and serum HBV DNA as well as HBsAg levels remain negative.

Discussion

Hemophilia B, or Christmas disease, is a sex-linked, recessive trait caused by mutations or deletions in the factor IX gene on the long arm of the X chromosome, resulting in coagulation factor IX deficiency [15, 17]. It is transmitted in 1–2 per 100,000 births and occurs approximately 25 % as frequently as hemophilia A or factor VIII deficiency [4, 10, 11, 13, 17]. The recognition of Christmas disease as a separate entity from hemophilia A did not occur until 1952, as the two were clinically indistinguishable [15].

The introduction in the 1960s of cryoprecipitate and later multidonor lyophilized intermediate purity factor IX and VIII concentrates for the treatment of hemophiliacs greatly ameliorated the course of the disease. The risk of viral infection, however, was also greatly increased, owing to the large number of donors required to produce the latter preparations [1, 3, 5, 6, 9, 14, 21, 22]. Studies performed in the 1980s revealed that 85 % of severe hemophiliacs had evidence of exposure to hepatitis B, and approximately 10 % had circulating HBV surface antigen [7–9, 14, 22, 24]. Liver biopsies performed on random groups of hemophiliacs in a prospective fashion have shown a 20 % incidence in chronic progressive liver disease [7, 8].

At present, with the advent of improved donor screening, the introduction of serologic testing for a wider variety of viral infections, and the development of better sterilization procedures such as solvent detergent techniques, dry heating, and immunoaffinity purification, the risk of viral transmission with coagulation factor replacement has been greatly reduced [5, 9, 17, 19, 22, 23].

Liver transplantation has been used to treat hemophilia A associated with end-stage liver disease since 1985. With the exception of genetic transmission, complete clinical resolution of hemophilia A has been shown to occur in such patients [2, 4, 12, 15, 16, 20]. Hepatic transplantation, however, has been recommended only in situations where there is concomitant cirrhosis, as the risks of this procedure and the lifelong immunosuppression outweigh the benefits in the absence of life-threatening liver disease [2, 20].

Factor IX is a vitamin K-dependent factor produced only in the liver. In 1974, transplantation of normal livers in hemophilic dogs was shown to reverse factor IX deficiency, resulting in levels increasing from below 1 % to above 90 % of normal values [25, 26]. Liver transplantation performed for hemophilia B associated with end-stage liver disease due to viral hepatitis has, to our knowledge, been reported in only two cases in the past [4, 15].

The movement towards the development of nonhuman and, thus, noninfectious coagulation factors by recombinant DNA technology, as well as novel approaches such as somatic cell gene therapy, will limit the need for liver transplantation in hemophiliacs in the future. In somatic cell gene therapy, normal factor IX is transferred in an appropriate expression vector into a target tissue, resulting in the production of biologically active factor IX in vivo [10, 13, 23]. At least 0.6 μg of factor IX per ml of plasma must be present in the bloodstream to be clinically significant [10]. To date, skin fibroblasts, hepatocytes, skeletal myoblasts, and endothelial cells have been tested as possible vectors for the production of recombinant factor IX [10, 13, 23].

As future developments continue in the treatment of hemophilia, there still remains a subpopulation of hemophiliacs with chronic liver disease as a result of past coagulation factor replacement who would benefit from liver transplantation.

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