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BRIEF REPORT

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Transmission of factor VII deficiency through liver transplantation

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Abstract The liver is the primary site of synthesis for the majority of coagulation factors. There are published accounts of liver donor-to-recipient transmission of protein C deficiency with dysfibrinogenemia and factor XI deficiency. In this article, we report what we believe to be the first observation, of transmission of factor VII deficiency, a rare, autosomal recessive coagulation disorder, from an affected liver donor to a naive liver recipient. At 300 days after transplantation, the recipient remains with an isolated prolongation of the prothrombin time and a below-normal level of factor VII, and has had no bleeding complications.

Key words Liver transplantation, factor VII deficiency · Factor VII deficiency, liver transplantation · Liver transplantation, disease transmission

Introduction

Orthotopic liver transplantation is a well established treatment both for liver failure and for correction of hepatic metabolic defects. Conversely, it is also possible to inadvertently transmit hepatic metabolic diseases to the recipient via a donor liver that harbors a genetic defect. Because the liver is the primary site of synthesis for the majority of coagulation factors, transplantation of a liver with a synthetic defect of a particular factor may confer a coagulopathy upon the liver recipient. There are published accounts of liver donor-to-recipient transmission of protein C deficiency with dysfibrinogenemia and factor XI deficiency [3, 4]. In the present article, we report what we believe to be the first case of transmission of factor VII deficiency, a rare, autosomal recessive coagulation disorder, from an affected liver donor to a naive recipient.

Case Report

The recipient was a 29-year-old female of Greek ancestry who had been diagnosed as having primary biliary cirrhosis (PBC) at the age of 27 years. Her medical history was significant for jaundice of unknown etiology at age 9 and ulcerative colitis at age 19. Neither she nor her family reported a history of bleeding disorders.

An extensive evaluation of the patient's medical records revealed a normal prothrombin time (PT) of 12.1 seconds (normal range 11.0–13.5) 10 years prior to transplantation, before the onset of her end-stage liver disease.

In December 1997, an ABO-compatible, non identical (donor A_2^+, recipient O^-), HLA-unmatched donor liver became available from a 63-year-old male as a result of an intracranial hemorrhage. The donor had a history of two previous cerebrovascular accidents (CVA) in 1996 and 1997. It is unknown whether the prior CVAs were hemorrhagic or ischemic. The donor's medical history was also significant for poorly controlled hypertension; his blood pressure on admission was 248/144 mmHg. Neither he nor his family had any known history of excessive bleeding. On admission, his liver function values were within normal limits, while his activated partial thromboplastin time (aPTT) of 21.1 seconds was also essentially within the normal (normal range 24–36 seconds). However, the PT was prolonged at 15.6 seconds. The serological tests for infectious agents were negative for HIV, HTLV, HBV, HCV, and RPR and positive for *Toxoplasma* and cytomegalovirus. The liver allograft was procured and preserved in the standard fashion and flushed and stored in University of Wisconsin solution.

The transplantation was unremarkable. A preperfusion biopsy of the donor liver revealed mild, mixed macro- and microvesicular steatosis with mild portal fibrosis. There was no aberrant vascular anatomy. The transfusion requirements were 16 units of packed red blood cells, 16 units of fresh frozen plasma (FFP) and 12 units of platelets. Total allograft ischemia time was 9.5 hours, with 58 minutes of warm ischemia. The immediate postoperative immunosuppressive regimen consisted of cyclosporine and methylprednisolone. Pathology of the explant revealed histologic features more consistent with primary sclerosing cholangitis than PBC.

The patient's liver function values peaked by postoperative day (POD) 3 (ALT 315 U/L, normal range 1–53 U/L; AST 280 U/L, normal range 1–50 U/L; total bilirubin 11.1 mg/dL, normal range 0.1–1.2 mg/dL) and began to normalize over the next several days. Her PT, however, continued to rise, remained at 25.5 seconds, and was not corrected with vitamin K therapy. Her aPTT returned to normal on POD 2. A mixing incubation study performed on POD 3 failed to identify a circulating anticoagulant. Hematologic analysis for coagulation factors revealed an isolated deficiency of factor VII (2.6 U/dL, normal range 50–150 U/dL) with normal levels of fibrinogen, factor V and factor X. No suitable pretransplantation blood samples were available from the donor or recipient for comparison of factor activity.

The patient underwent multiple liver biopsies (POD 9 and 17) for severe, steroid-resistant acute rejection. She responded well to treatment with OKT3, corticosteroids, and mycophenolate mofetil (MMF), and her IL-2 blocker was switched to tacrolimus. Her subsequent hospital course was uneventful. She was discharged home on POD 32 and is alive and well at 300 days. Her maintenance immunosuppression regimen consists of tacrolimus, prednisone and MMF. She reports no episodes of abnormal bleeding. Her liver function values have all remained within normal limits since the time of her treatment with OKT3 for rejection. Her PT remains prolonged, namely, between 17 and 19 seconds. Repeat factor VII assay (12 U/dL), mixing incubation study (immediate correction of PT with normal serum) and Russel viper venom test (17 seconds, control 17 seconds) performed approximately 3 months after transplantation all suggest persistent, isolated factor VII deficiency.

We attempted to contact the donor's family through the local organ procurement organization to notify them of the possibility of a factor deficiency among family members. Although the presence of factor VII deficiency with a family member would further substantiate our case, our attempts to reach the family were unsuccessful.

Discussion

Successful liver transplantation requires the selection of healthy donor organs. One complication occurring with head-injured donors is that large amounts of tissue thromboplastin are released, which may cause hemostatic activation with abnormalities in PT and aPTT [9]. In such circumstances, it can be difficult to detect pre-existing synthetic defects of coagulation factors in the donor livers. The donor in this case had no known bleeding disorders, but had a history of three CVAs, the last one hemorrhagic. His history of poorly controlled hypertension was thought to be the major factor contributing to this final CVA episode. The prolonged PT on admission was thought to be incidental to his cerebral insult. Therefore, no further evaluation was performed.

Factor VII, synthesized in the liver, is a vitamin-K-dependent coagulation factor and is a component of the extrinsic coagulation pathway. The accepted model of coagulation suggests that calcium and factor III (tissue factor, released upon tissue damage) activate factor VII and initiate a cascade including factors X, IX, VIII, V, II and I. The final product of the cascade is the formation of a fibrin clot. Several of these factors are part of the "common" pathway of coagulation and are measured by both PT and aPTT. Because factor VII activity is observed primarily in the extrinsic pathway, an isolated deficiency manifests itself as a prolonged PT with a normal aPTT.

Reversible, transient factor VII deficiency has been shown to be caused by several mechanisms. Acquired vitamin K deficiency is a common complication of liver disease and may temporarily present as an isolated prolonged PT due to the short half-life (3–6 hours) and rapid depletion of factor VII. The deficiency is highly responsive to supplemental vitamin K therapy. Since our patient did not respond to vitamin K supplements, we assume her persistently elevated PT does not result from nutritional deficit. In the case of certain lung cancers, isolated deficiency of factor VII has been reported as a paraneoplastic syndrome thought to be caused by the formation of an inhibitor [8]. Our patient is not known to have lung cancer, and no inhibitor was detected. In a small, prospective study, severe systemic sepsis has been shown to produce a reversible, non-inhibitor-induced factor VII deficiency through an unknown mechanism [2]. However, our patient was never septic. Transient liver failure can cause a factor VII deficiency which resolves as liver function improves. Indeed, factor VII activity, PT and protein C antigen have been shown to be early prognostic indicators of liver recovery or failure after liver transplantation [7]. Our patient did not suffer liver failure in the postoperative period. She did experience severe rejection requiring OKT3 treatment, but well after her recovery from this rejection episode, her factor VII level remains below the normal range.

Organs from blood group A_2 donors are known to be less antigenic than organs from A_1 donors, and are similar to those from O donors. Successful transplantation of A_2 kidneys to nonidentical patients has been reported on [6]. At our center, we have performed without complications 6 liver transplantations on blood group 0 recipients using organs from A_2 donors [5]. There are no accounts of patients developing factor deficiencies after ABO-compatible-mismatch solid organ transplantations. It is unlikely that this was a contributing factor in this case.

With respect to the patient presented here, there was no history of a pre-existing bleeding diathesis or factor deficiency. In addition, she had a normal coagulation profile documented prior to her liver failure. Since liver transplantation, the recipient has had an isolated prolonged PT, a persistently decreased factor VII level, and no measurable circulating anticoagulant. While the presence of factor VII deficiency in a donor's relative would further substantiate our case, we were unable to contact and test the donor's family. Although the evidence is indirect, and we have no pretransplant factor VII levels for either the donor or the recipient, we attribute this patient's factor VII deficiency to her donor liver.

Congenital deficiency of factor VII is an extremely rare, autosomal recessive disorder occurring in approximately 1/500000 people. The expression of this disease is highly variable. In mildly affected individuals, the disease may be completely asymptomatic and discovered only during routine blood testing as an isolated, prolonged PT. More significant bleeding episodes, such as intracranial hemorrhage or hemarthroses, may be associated with severe deficiency or activity levels of less than 1 % [10].

Bleeding diathesis in factor VII deficiency has been reported to correlate poorly with plasma factor VII coagulant activity [10], and factor levels of between 10 and 25 % have been described as sufficient for adequate hemostasis [1]. It has been suggested that raising plasma factor VII levels to 1.0 U/dL will stop most bleeding episodes and that levels above 2.0 U/dL may be adequate for most surgical procedures [11]. The patient reported on in the present article currently has a plasma factor VII level of 12 U/dL with no evidence of excessive bleeding episodes or abnormal menses. Based on previous accounts, this appears to be an adequate level of factor VII to insure the patient's safety against an increased risk of bleeding. However, should she require a surgical procedure or be at risk of bleeding, then treatment with FFP and/or factor VII concentrates may be indicated. Recombinant, activated factor VII (factor VIIa) has been used in several clinical trials to treat factor VII deficiency and may be useful in the future [1].

Summary

A complete donor history along with a laboratory evaluation of hepatic synthetic function and a coagulation profile remain important elements in determining the suitability of livers for transplantation. Time constraints during the peritransplantation period preclude a thorough screening evaluation for inborn errors of metabolism. The presence of an isolated prolongation in the prothrombin time, with or without a bleeding history, can signal an isolated factor VII deficiency. Livers from donors with known or suspected factor VII deficiencies must be evaluated cautiously, and extra serum samples should be taken and stored for possible future evaluation. In the absence of a history of abnormal bleeding in the donor or the donor's family, an isolated, prolonged PT should not be a contraindication to use of the donor's liver for transplantation.

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