To the editor:

Extrahepatic factor VIII production in transplant recipient of hemophilia donor liver

Table 1. Coagulation studies before and after orthotopic liver transplantation

<table>
<thead>
<tr>
<th>FVIII:C, U/mL</th>
<th>APTT, seconds</th>
<th>PT/INR, seconds</th>
<th>VWF:Ag, U/mL</th>
<th>VWF:RCo, U/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor</td>
<td>0.05</td>
<td>98.8</td>
<td></td>
<td>2.36</td>
</tr>
<tr>
<td>Recipient</td>
<td>Pre-OLTX</td>
<td>1.23</td>
<td>31.7</td>
<td>16.5/1.4</td>
</tr>
<tr>
<td></td>
<td>Day 1 post-OLTX</td>
<td>0.48</td>
<td>49.5</td>
<td>21.8/2.9</td>
</tr>
<tr>
<td></td>
<td>Day 2 post-OLTX</td>
<td>1.04</td>
<td>36.6</td>
<td>17.4/1.4</td>
</tr>
<tr>
<td></td>
<td>Day 8 post-OLTX</td>
<td>1.69</td>
<td>33.6</td>
<td>15.6/1.3</td>
</tr>
<tr>
<td></td>
<td>Day 110 post-OLTX</td>
<td>1.38</td>
<td>98.8</td>
<td>37.4/3.6</td>
</tr>
</tbody>
</table>

Although the liver is the major site of production of factor VIII (FVIII), as demonstrated by correction of hemophilia A by liver transplantation,1 extrahepatic FVIII production has been suspected ever since increased FVIII levels were recognized in end stage liver disease.2,3 Extrahepatic FVIII production has been confirmed by FVIII mRNA detection in spleen and kidneys of a pig model of fulminant liver failure,4 the correction of hemophilia in animal models after spleen or lung transplantation,5,6 and normal FVIII levels in normal canine recipients of hemophilia A dog livers.7,8 In humans, FVIII:C levels have been detected in pulmonary endothelial cell supernatants.9 Although obligate carrier donor liver transplantation corrects hemophilia,10 extrahepatic FVIII production in humans has not been demonstrated. We report normal FVIII production after transplantation of a hemophilia A donor liver into a nonhemopholic recipient with alcoholic cirrhosis.

The liver donor was a 47-year-old white man with mild hemophilia A, FVIII:C = 0.05 U/mL, hypertension, and insulin-dependent diabetes mellitus complicated by renal failure and peripheral vascular disease. He experienced recurrent hemarthroses and a Mallory Weiss tear, managed uneventfully with FVIII concentrate. He presented to the emergency room with a gastrointestinal bleed, complicated by hypovolemic shock and diabetic ketoacidosis, and died several days later with irreversible diffuse anoxic brain injury. There was no factor VIII inhibitor.

The liver recipient was a 69-year-old white man with alcoholic cirrhosis and stage 2 hepatocellular carcinoma. His Model for End-Stage Liver Disease (MELD) score was 25, following a 3-month wait on the transplant list. His FVIII level was normal preoperatively and remained so postoperatively (Table 1). The activated partial thromboplastin time (APTT) was subsequently markedly prolonged from heparin therapy for hemodialysis, and both prothrombin time (PT) and APTT were prolonged from vitamin K deficiency due to warfarin therapy for atrial fibrillation, and intravenous antibiotic agents for pneumonia. Postoperatively, his course was complicated by acute respiratory distress syndrome, biliary stricture, encephalopathy, and cytomegalovirus (CMV) viremia, conditions likely accounting for nonspecific elevation of von Willebrand factor (VWF). His graft function was good, with normal total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels and no evidence of liver failure.

This report demonstrates for the first time that transplantation of a human hemophilia A donor liver results in normal FVIII levels after transplantation. The postoperative persistence of normal FVIII levels in the hemostatic range confirms that the source of recipient FVIII production is other than liver tissue. Whether the source is lung, spleen, kidney, or other tissue, however, is not possible to confirm in this recipient. It is of interest that transplantation of spleen or lung has corrected factor VIII deficiency in hemophilia animal models,5,6 and human lung endothelial cells produce FVIII,7 but whether lung tissue compensates for absent hepatic FVIII production remains unanswered.

Together with these reports, these data support the existence of human extrahepatic FVIII production that compensates for missing hepatic FVIII production. Further study will be required to determine which tissues contribute to human extrahepatic FVIII production.

Potential ethical issues regarding the donor and recipient warrant comment. Although liver donors to date have not included persons with hemophilia, increasing evidence in animal models5,6 suggests the success of such an approach in humans. In this case, however, a diagnosis of hemophilia remained unclear before transplantation. Regarding the recipient, liver transplantation is increasingly performed in elderly patients, and the presence of hepatocellular carcinoma (stage 1 or 2) increases priority for transplantation, as survival with transplantation is superior to survival with other forms of treatment.

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References

To the editor:

Rapid resolution of GVHD after orthotopic liver transplantation in a patient treated with alefacept

Graft-versus-host disease (GVHD) after transfusion of nonirradiated blood products or solid tumor transplantation is a rare but lethal complication associated with mortality of 80% to 90%1-3 and occurs when immunocompetent donor T cells from the graft recognize disparate alloantigens of host cells. This process occurs primarily in immunocompromised hosts. Symptoms are typical of GVHD affecting skin, gut, and liver. Profound pancytopenia due to graft-versus-hematopoiesis effect may occur, described in animal models of transfusion-associated GVHD.4 Therapies to reverse this process are almost uniformly unsuccessful.1 Case reports and small series have documented response with agents such as basiliximab, daclizumab, antilymphocyte antibodies, and granulocyte colony-stimulating factor (G-CSF), though response to these agents is inconsistent.1,5-6

Our patient was a 60-year-old man with cirrhosis status postorthotopic liver transplantation (OLT). At day 20 after OLT the patient reported abdominal pain and emesis and had a fever. His white blood cell count (WBC) was 11.3 k/μL (ANC of 8.89 k/μL), hematocrit was 31%, and platelet count was 337 k/μL. Infectious workup and empiric antibiotics were started. At day 27 the patient developed a generalized, dusky morbilliform rash with reticulated morphology (biopsies showed cytotoxic dermatitis compatible with GVHD grade 2-3) and odynophagia (laryngoscopy revealed mucositis). His WBC nadired to 0.02 k/μL on day 39 (Figure 1). A bone marrow biopsy revealed marked hypocellularity (<10%) with residual hematopoiesis showing apoptotic bodies, consistent with GVHD. To secure the diagnosis of alloantigen-induced marrow aplasia, 4 specimens were submitted for single tandem repeat (STR) analysis5: (1) a buccal swab (recipient DNA); (2) donor DNA–Allogen labs; (3) peripheral blood; and (4) T-cell enriched fraction from peripheral blood. Peripheral blood DNA showed mixed chimerism (11% donor DNA), and the T-cell-enriched fraction (81% donor DNA) confirmed the diagnosis of GVHD. The patient remained profoundly pancytopenic despite high-dose steroids, filgrastim support, and rabbit antithymocyte globulin.1,5 Because of the patient’s deteriorating condition and lack of response to other therapies, his case was discussed in the transplantation peer review group. Off-label use of the immunosuppressant alefacept was recommended. Rationale and potential side effects were discussed with the patient, who gave consent and subsequently received 30 mg alefacept, followed by 3 additional doses of 30 mg every 3 days. After the initial alefacept dose, his blood counts improved over 9 days to a WBC of 7.49 k/μL and platelet count of 31 k/μL. His counts remain stable 13 months later. It is provocative to note the rapidity and durability of his response after alefacept dosing.
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