Case Report

Hepatic veno-occlusive disease related to tacrolimus after pancreas transplantation

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Abstract

Hepatic veno-occlusive disease (HVOD) describes the nonthrombotic, fibrous obliteration of the small centrilobular hepatic veins by connective tissue and centrilobular necrosis in zone 3 of the acini. Occlusion of the terminal venules of the liver might result in HVOD with the characteristic clinical findings of painful hepatomegaly, ascites, jaundice, and weight gain in more than 5% of patients. It is mainly observed after hematopoietic stem cell transplantation (SCT) and is responsible for significant morbidity and mortality. The incidence of HVOD is much lower after solid organ transplantation than after SCT and seems to differ from one organ to another. It has been sporadically reported after lung, renal, and liver transplantation, but has never been reported after pancreas transplantation. In general, HVOD is presumably attributed to azathioprine or tacrolimus used in solid organ transplantation. Here we describe a case of HVOD occurring after pancreas transplantation, in which tacrolimus might have played a causative role because complete recovery was observed after discontinuation of tacrolimus. Pancreas transplantation physicians should raise the suspicion of HVOD when a recipient presents with hepatomegaly, ascites, or jaundice.

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1. Introduction

Hepatic veno-occlusive disease (HVOD) is a distinct clinical entity describing the nonthrombotic, fibrous obliteration of the small centrilobular hepatic veins by connective tissue and centrilobular necrosis in zone 3 of the acini.1–3 Based on recent work suggesting that sinusoidal changes are primary events in the pathology of the disease, the term sinusoidal obstruction syndrome is considered to better describe the condition.4 Occlusion of the terminal venules of the liver might result in HVOD with the characteristic clinical findings of painful hepatomegaly, ascites, jaundice, and weight gain in more than 5% of patients.2–8

HVOD was first described in Jamaicans who had consumed large amounts of Senecio plants in the form of “bush tea” containing pyrrolizidine alkaloids.2 This disease is also well known to be associated with Mylotarg, a monoclonal anti-CD33 antibody gemtuzumab ozogamicin used for acute myelogenous leukemia, and is now mainly observed in patients with hematopoietic stem cell transplantation (SCT) following the administration of various chemotherapeutic agents such as actinomycin D, mithramycin, dacarbazine, cytosine arabinoside, and 6-thioguanine.2,3 However, HVOD has also been reported after solid organ transplantation, but much less frequently. In general, the disease is presumably attributed to azathioprine2,9–12 or tacrolimus1,6 used in solid organ transplantation. Cases have been sporadically described after lung,1,6 renal,2,9–13 and liver4–18 transplantation, but have never been reported in the literature after pancreas transplantation. Here, we report a case of HVOD occurring after pancreas transplantation, in which tacrolimus might have played a causative role.
2. Case report

A 25-year-old female began to suffer from type 2 diabetes mellitus at the age of 11 years and had experienced uremia under hemodialysis for 3 years. She underwent simultaneous pancreas and kidney transplantation on June 30, 2009, with one mismatch for human leukocyte antigen typing and 84.5% panel reactive antibody level for Class I and 31.84% for Class II, but a negative pretransplant lymphocytotoxic crossmatch. Unfortunately, primary nonfunction of the kidney graft occurred because of a technical complication with the occlusion of the renal artery, and the failed kidney graft was explanted on postoperative day 1. Immunosuppressive therapy included basiliximab (Simulect, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA) for induction (given on postoperative day 0 and day 4), and tacrolimus (Prograf, Astellas Pharma US, Inc., Deerfield, IL, USA), Myfortic (enteric-coated mycophenolic acid; Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA), and prednisolone for maintenance therapy. Prednisolone was tapered and withdrawn completely 3 months after transplantation. The target trough level for tacrolimus was $6 - 15 \text{ ng/mL}$.

Approximately 9 months after transplantation, this patient reported development of fever, mild right abdominal pain, and an increase in abdominal girth. The fever subsided spontaneously without known cause. The pancreas graft had been functioning well without evidence of rejection or pancreatitis (fasting blood sugar: 85 mg/dL, c-peptide: 9.79 ng/mL, amylase: 85 U/L, lipase: 22 U/L). The laboratory data showed leukopenia (1600/mm$^3$) and thrombocytopenia (8900/mm$^3$). The computed tomography (CT) scan showed pictures of HVOD with hepatomegaly, massive ascites, periportal edema, diffuse mottled hepatic enhancement, and patent hepatic veins (Fig. 1). The periportal edema and diffuse mottled hepatic enhancement, in addition to the signs of portal hypertension, might have suggested sinusoidal stasis. The inferior vena cava was patent by CT scan. There was no evidence of heart failure by chest X-ray image study and clinical feature. An initial liver biopsy attempt was aborted owing to significant coagulopathy and massive ascites. Meanwhile, a massive bloody stool occurred during hospitalization. The angiography showed a pseudoaneurysm with bleeding from a branch of the ileocolic artery. The cause of the pseudoaneurysm was not known, but did not seem to be related to the HVOD. The bleeding was eventually stopped by transarterial embolization and correction of the coagulopathy.

Tacrolimus was discontinued and replaced by cyclosporine (Novartis Pharmaceuticals Corporation) with a target trough level of 200–300 ng/mL. Otherwise, no alternation of other medications was made. Three months after discontinuing tacrolimus, there was resolution of the patient HVOD demonstrated by CT scan (Fig. 1C). All the blood cell counts also returned to normal level. These observations might lead to the conclusion that tacrolimus could be the causative agent for HVOD in this case.

3. Discussion

HVOD is mainly observed after hematopoietic SCT and may be responsible for significant morbidity and mortality. The incidence of HVOD after hematopoietic SCT is variable, ranging from 10% to 60%.$^{4,5}$ The number of reported HVOD cases after solid organ transplantation is rather low, and most of them are sporadically reported, with an incidence of 1.9–2.5% after kidney transplantation, and HVOD cases seem to differ from one organ to another.$^{1,2,6,9}$ In these reports, HVOD is generally linked to the administration of azathioprine.$^{2,10-12}$ Tacrolimus, a calcinurin inhibitor, is currently one of the most common potent immunosuppressants used in organ transplantations. Although tacrolimus undergoes hepatic metabolism, only mild hepatotoxicity has been reported with its use. Nevertheless, HVOD induced by tacrolimus has also been reported, but less commonly as compared to that by azathioprine.$^1$

The classical characteristics of painful hepatomegaly, ascites, jaundice, and weight gain for more than 5% of patients has been described in HVOD.$^2$–$^8$ but the clinical diagnosis of HVOD is usually difficult because the symptoms and signs of

Fig. 1. A 25-year-old female with hepatic veno-occlusive disease after pancreas transplant. Post contrast-enhanced coronal reformatted computed tomography (CT) images shows (A) a normal homogenous enhancement of the liver and a pancreas graft surrounded by a small amount of fluid in the right lower abdomen with head-up position 2 weeks after pancreas transplant; (B) hepatomegaly, ascites, periportal edema, and diffuse mottled hepatic enhancement suggestive of sinusoidal stasis with patent hepatic veins and gallbladder edema (not shown) about 8 months after pancreas transplant; and (C) hepatic parenchymal enhancement returned to homogenous 3 months after tacrolimus was discontinued and replaced by cyclosporine.
this condition often overlap with similar hepatic injury states.\textsuperscript{1,4,5} As shown in our case, an abdominal CT showing periportal edema and diffuse mottled hepatic enhancement, in addition to the signs of portal hypertension, might suggest the occlusive patterns of small centriflobular hepatic veins and could lead to the diagnosis of HVOD for transplant patients at risk. Some authors claimed that a hepatic ultrasound showing the detection of reversed blood flow in the segmental branch of the portal vein using color flow Doppler may be also helpful in the diagnosis of HVOD.\textsuperscript{2,3} For clinically suspected cases, liver biopsy for histological examination would be the gold standard to confirm the diagnosis. Liver biopsies may reveal dilated sinusoids and hepatic necrosis with sclerosis of the venular walls and intense collagen deposition in the sinusoids, which eventually lead to obliteration of the venules, extensive hepatocellular necrosis, and fibrous replacement of the hepatic tissue.\textsuperscript{1,4,5} The reason that a percutaneous liver biopsy is not always suitable for patients with HVOD is because most of them present with ascites and the associated hemostatic disorders, as in our case. Therefore, the liver biopsy could be done by transjugular approach. Meanwhile, a measurement of the wedged hepatic venous pressure gradient of 10 mmHg taken at the time of the transjugular biopsy provides additional clues and has a 91% specificity, 52% sensitivity, and 86% positive predictive value in the diagnosis of HVOD.\textsuperscript{5}

Currently, little information is available on the treatment of HVOD. Several approaches have been tried, but none is uniformly effective. Nevertheless, as shown in our case, early withdrawal of causative immunosuppressants such as azathioprine and tacrolimus seem to be the key.\textsuperscript{1,2,6} The lack of an effective therapy for HVOD has spurred much interest in finding potential medications to prevent the disease, such as low-molecular-weight heparin, ursodeoxycholic acid, and pentoxifylline (a xanthine derivative).\textsuperscript{2} Prognosis depends on the severity of the hepatic injury and dysfunction. Mild disease is defined by no significant adverse effect from liver dysfunction and is often self-limited and resolves without treatment after the offending agent is withdrawn. Moderate disease is characterized by liver dysfunction requiring therapy for control of symptoms such as diuresis for abdominal distension due to fluid retention and analgesia for pain due to hepatomegaly, but with eventual complete resolution. By contrast, while most patients with HVOD fall into the mild to moderate category, a significant fraction will develop severe HVOD characterized by a nonresolving disease process, which is often associated with a dismal outcome eventually requiring liver transplantation.\textsuperscript{4,5}

In conclusion, this case of HVOD after pancreas transplantation with immunosuppressive therapy is the first reported in the literature. The causative agent was presumed to be tacrolimus since complete recovery was observed after discontinuation of tacrolimus. Pancreas transplantation physicians should raise the suspicion of HVOD when a recipient presents with hepatomegaly, ascites, or jaundice.

References