Pulmonary Hypertension Post Liver-Kidney Transplant

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ABSTRACT

Porto-pulmonary hypertension has been recently recognized in patients post-liver transplantation with or without pre-transplant hepatopulmonary syndrome. We present a unique case of pulmonary hypertension in a 65-year-old patient after simultaneous liver-kidney transplantation for cirrhosis secondary to chronic hepatitis C infection and alcohol use disorder and end-stage renal disease secondary to diabetic nephropathy. He presented to pulmonary hypertension clinic with progressive shortness of breath and elevated right-sided pulmonary pressures on echocardiogram. He did not have pre-transplant hepatopulmonary syndrome and his post-transplant liver and kidney functions were normal. His right heart catheterization showed normal capillary wedge pressure, elevated mean pulmonary artery pressure and high pulmonary vascular resistance with normal cardiac index. His symptoms and pulmonary pressures improved with ligation of AV fistula.

KEYWORDS: pulmonary hypertension, liver transplant, renal transplant, simultaneous liver-kidney transplant, post-transplant pulmonary hypertension

INTRODUCTION

Portopulmonary hypertension (PoPH) de novo after liver transplantation has been recognized recently either with or without pre-transplant hepatopulmonary syndrome (HPS).[1,2] There are no reports of pulmonary hypertension occurrence following simultaneous liver-kidney transplants, which is becoming a more common procedure. We present a unique case of heart failure and pulmonary hypertension (PH) after simultaneous liver-kidney transplants in a patient, whose pulmonary artery pressures improved during post-transplant course without use of pulmonary arterial hypertension (PAH) specific therapy, but with arteriovenous (AV) fistula closure.

CASE PRESENTATION

A 65-year-old male was referred to pulmonary hypertension clinic for evaluation of exertional dyspnea and elevated pulmonary pressures on echocardiogram 9 months after simultaneous liver-kidney transplants. The patient received deceased donor simultaneous liver-kidney transplants for liver cirrhosis (secondary to chronic hepatitis C infection and alcohol use) and end-stage renal disease (secondary to diabetic nephropathy). The patient's medical history was significant for systemic hypertension, diabetes mellitus with diabetic nephropathy and neuropathy and permanent atrial fibrillation. The patient had quit drinking and smoking 8 years ago after 50-pack years and had denied any illicit substance use since then. His pre-transplant course was complicated by portal hypertension, ascites and variceal bleeding requiring band ligation and hepatocellular carcinoma treated with radiofrequency ablation. His pre-transplant echocardiogram showed normal left ventricular systolic function (Ejection Fraction- 65–70%) with severe left atrial dilatation, moderately dilated right ventricule with normal systolic function (tricuspid annular plane systolic excursion 2.1 cm). A pre-transplant right heart catheterization had demonstrated borderline pulmonary hypertension with a normal pulmonary vascular resistance (PVR), but an elevated cardiac index (**Table**).

Table. Summary of Right Heart Catheterization Results

	Pre-Transplant	Post-Transplant	Post AVF closure
Right Atrial Pressure (mm Hg)	10	11	4
Right Ventricular Pressure (mm Hg)	38/10	47/11	27/5
Pulmonary Artery Pressure (mm Hg)	38/14 (22)	49/21 (31)	29/11 (19)
Pulmonary Capillary Wedge Pressure (mm Hg)	14	15	12
Cardiac Output (L/minute)	8.0 (TD) 9.7 (F)	4.55 (TD) 4.75 (F)	3.4 (F)
Cardiac Index (L/minute/m2)	4.17 (TD) 5.05 (F)	2.25 (TD) 2.35 (F)	1.73 (F)
Pulmonary Vascular Resistance (Woods Unit)	1.0	3.67	2.1
Systemic Vascular Resistance (Woods Unit)	7.75	12.45	25.31

Abbreviations: AVF; arteriovenous fistula, F; Fick' s method, TD; Thermodilution

Two months after uncomplicated liver-kidney transplant, the patient reported shortness of breath after walking about 20 feet, abdominal distension and leg swelling. He had experienced a weight gain of as much as 30 pounds above his pre-transplant weight and he was also noted to have pleural effusion. Laboratory values for his liver (Total bilirubin 1.2 mg/dl, Aspartate aminotransaminase 15 Units/L, Alanine aminotransaminase 12 Units/L, Alkaline phosphatase 101 Uniy/L) and kidney functions were normal. He was started on oral furosemide with some improvement in his symptoms along with a decrease in body weight. His transthoracic echocardiogram showed normal left ventricular systolic function with (Ejection Fraction 65–70%), mild concentric left ventricular hypertrophy, severe bi-atrial enlargement, normal right ventricular size and function (tricuspid annular plane systolic excursion 2.4 cm), moderate to severe tricuspid regurgitation with estimated right ventricular systolic pressure 50–60 mm of Hg, an increase from pre-transplant estimates. He underwent a right heart catheterization at this time which showed pulmonary hypertension with a cardiac index 2.35 L/minute/m^2, mean pulmonary artery pressure 31 mm Hg, pulmonary capillary occlusion pressure of 15 mm Hg and pulmonary vascular resistance of 3.67 Woods units consistent with pulmonary hypertension with a pre-capillary component (**Table**). Post-right heart catheterization, while on twice daily furosemide, he reported that he could walk one mile on alternate days without any dyspnea, and reported improved orthopnea and leg swelling, though his weight remained about 20 pounds above his pre-transplant weight. His medications at this time included aspirin 81 mg, cholecalciferol 2000 units, ferrous sulfate 325 mg, furosemide 60/40 mg, gabapentin 600mg three times daily, Insulin glargine 15 units bedtime and aspart 4 units three times daily, omeprazole 20 mg, quetiapine 25 mg bedtime, co-trimethoprim-sulfamethoxazole 400/800 mg and tacrolimus 2/1 mg daily. Physical examination showed jugular venous distension of ~9 cm of water, a palpable thrill over right supraclavicular region with dilated veins around a right arm AV fistula, an irregularly irregular pulse, mildly decreased air entry in right lower lung and 1+ pitting edema. His arterial blood gases prior to (pH-7.52, pCO_2-25 mmHg, pO_2-92 mmHg, $SatO_2$-98% and HCO_3-20.4 mEq on room air) and after (pH-7.44, pCO_2-44 mmHg, pO_2-81 mmHg, $SatO_2$-96% and HCO_3-29.9 mEq on room air) transplantation did not show any evidence of hypoxia. His liver enzymes post-transplantation were normal work up for pulmonary hypertension including serologic tests for connective tissue diseases, chest imaging, pulmonary function tests (forced expiratory volume-84% of predicted and forced vital capacity-92% of predicted without any bronchodilator response) and ventilation-perfusion scan was unremarkable. Given his abnormal examination findings and history suggesting possible high output failure, he was referred for closure of his AV fistula. After closure of his AV fistula, the patient's shortness of breath improved over the course of several months without further intervention. A repeat right heart catheterization showed a decrease in cardiac index to 1.73 L/minute/m^2, mean pulmonary artery pressure to 19 mm Hg, pulmonary capillary occlusion pressure 12 mm Hg and PVR to 2.1 Woods units (**Table**). The patient is now able to walk 2 miles every day without any difficulty and his furosemide has been titrated down to 20 mg/day.

DISCUSSION

Our patient developed symptomatic pulmonary hypertension and heart failure following simultaneous liver-kidney transplants, in the absence of pre-existing HPS, and despite some improvement in hyperdynamic circulation after transplant. He then improved symptomatically and hemodynamically over the course of several months following AV fistula closure.

Development of de novo PH has been reported in 14 patients post-orthotropic liver transplant (OLT).[1,2] It can occur in 3 settings, 1) presence of pre-OLT HPS, 2) recurrent cirrhosis with PoPH and 3) isolated PoPH without any prior HPS.[3] Development of PoPH after liver transplant varies in different patients. Patients with prior HPS may develop PoPH usually within 1 year of OLT, whereas it may take years to develop in patients with recurrent acquired liver disease. Aucejo et al. proposed 2 mechanisms to explain PoPH in patients with HPS, 1) resolution of HPS and hence decrease in intrapulmonary vasodilation, and 2) hyperdynamic pulmonary circulation with arteriolar remodeling leading to increased PVR.[2] Both these processes make diagnosis of PoPH difficult, until post operatively. Acquired recurrent liver disease leads to portal hypertension and subsequent PoPH years after OLT. There is no clear etiology behind development of PoPH in patients without antecedent HPS or recurrent liver disease. It is not clear either if PoPH in these patients was idiopathic or as result of organ transplant. Unique to mechanisms discussed above, our patient developed PH within months after OLT in absence of pre-OLT HPS and post-OLT liver disease and does not clearly fall in the category of PoPH.

Prognosis of new PH post-liver transplant is poor regardless of predisposing etiology.[4] Patients with delayed onset have relatively better prognosis than patients who have earlier recognition of PH. Prostacyclin, prostacyclin analogues, phosphodiestrase inhibitors and endothelin receptor antagonists have been used in treatment of pre-transplant PH with improvement in 6-minute walk distance, New York Heart Association (NYHA) functional class and survival rates.[5-9] Liver transplant improves or completely normalizes pulmonary pressures in certain patients.[10,11] Post-OLT de novo PH poses a different challenge for treatment of disease with poor prognosis. Endothelin receptor antagonists have been shown to have better outcomes in pre-transplant

PH patients, but there may be a concern to starting these agents in liver-transplant patients due to potential hepatotoxicity.[5,9,12] Experimental studies have shown that tacrolimus reverses endothelial dysfunction in PAH patients by activating bone morphogenic protein receptor 2 (BMPR 2) by signaling pathway.[13] Safety of low dose (target trough levels 2-5 ng/mL) tacrolimus (FK506) has been tested in a Phase IIa trial of PAH patients increase in levels of BMPR 2 (low in PAH).[14] Spiekerkoetter et al. in a case series of 3 end-stage PAH patients showed that treatment with low dose Tacrolimus increased circulating BMPR2 levels with improvement in 6-minute walk test, NYHA class and freedom from hospitalization from right ventricular failure.[15] Dose-dependent increase in BMPR2 was noticed in a proof-of- concept study to establish safety of Tacrolimus use in PAH patients.[14] However, the role of immunosuppressive dose of tacrolimus in mitigating post-transplant PAH remains unknown.

Pulmonary hypertension has also been identified in patients with end-stage renal disease undergoing hemodialysis.[16-18] Increased pulmonary vasoconstriction leading to increased vascular resistance and high output failure associated with AV fistula have been reported as possible explanations for pulmonary hypertension in these patients.[19-22] Hyperdynamic circulation causes increased shear stress and high pressure in pulmonary arteries with normal pulmonary vascular resistance initially. Increased endothelin-1 (ET-1) and endothelin receptor-A have been reported in lung tissue with high blood flow in animal studies.[23,24] Endothelin-1 is a potent vasoconstrictor and causes vascular smooth muscle cell hyperplasia. Significant correlation was reported between elevated ET-1 levels, pulmonary arterial pressures and pulmonary blood flow in newborns with systemic-to-pulmonary shunts. Correction of high blood flow has led to reversal of pulmonary vascular remodeling in animal models.[25] Renal transplant has been associated with improvement in pulmonary hypertension.[26] Our patient did not have any evidence of PoPH or HPS prior to liver-kidney transplants. He developed PH with elevated PVR within months post-OLT which is unique to previously reported cases of PoPH which has been reported in following settings 1) pre-transplant PoPH or HPS, 2) recurrent cirrhosis with PoPH or 3) isolated PoPH without any prior HPS. It is possible that in our patient, a persistent hyperdynamic circulation from a patent AV fistula led to pulmonary vascular remodeling with improvement after closure of AV fistula. Unfortunately, our patient did not undergo mean shunt flow measurement prior to or during ligation of AV fistula to evaluate if it was reason for high output state. But his cardiac output decreased from 4.9 L/minute to 4.5 L/minute with occluding local pressure on right heart catheterization prior to AV fistula ligation suggesting minimal flow through fistula. Additionally, patient did not have hemodynamics performed with exercise or with fluid challenge, which leaves heart failure with preserved ejection fraction as unaddressed differential diagnosis. Nonetheless, he does not have reported abnormal LV diastolic function on echocardiogram at rest and his filling pressures are normal as well. The number of simultaneous liver-kidney transplants has grown over the years and simultaneous liver-kidney transplant occurred in 8.2% of all liver transplants in 2014. Recognition of PH and addressing all factors potentially responsible for PH in this special patient population is important.

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