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Venous outflow obstruction and portopulmonary hypertension after orthotopic liver transplantation

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Female, 54
Final Diagnosis: Suprahepatic inferior vena cava anastomosis stricture
Symptoms: Ascites • fatigue • lower limb edema • hepatomegaly
Medication: —
Clinical Procedure: —
Specialty: Transplantology • Critical Care Medicine

Objective: Unusual clinical course

Background: Suprahepatic inferior vena cava anastomosis stricture is an unusual vascular complication after orthotopic liver transplantation with the "piggyback" technique. Clinical manifestations are dependent upon the severity of the stenosis. Portopulmonary hypertension after orthotopic liver transplantation is a complication that carries high mortality due to cardiopulmonary dysfunction. The pathogenesis of pulmonary vascular disorders after orthotopic liver transplantation remains uncertain.

Case Report: We report a case of acute right heart pressure overload after surgical correction of the suprahepatic inferior vena cava anastomotic stricture in a 54-year-old woman who had preexisting pulmonary arterial hypertension associated with portal hypertension after orthotopic liver transplantation. Twenty months posttransplantation, she developed fatigue and progressive ascites. On admission, the patient had hepatomegaly, ascites, and lower limb edema. Symptoms in the patient developed gradually over time.

Conclusions: Recurrent portal hypertension by vascular complications is a cause of pulmonary arterial hypertension after orthotopic liver transplantation. Clinical manifestations of suprahepatic inferior vena cava anastomotic stenosis are dependent upon their severity. Sildenafil is an effective drug for treatment of pulmonary arterial hypertension after portal hypertension by vascular complications.

Key words: liver transplantation • suprahepatic inferior vena cava • portopulmonary hypertension • pulmonary arterial hypertension • acute cor pulmonale

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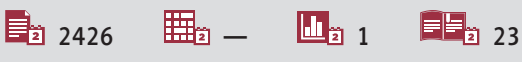

Background

Venous complications are infrequent after orthotopic liver transplantation (OLT). The incidence rate of venous complications involving the vena porta is 2.7% after OLT, whereas incidence rate of complications of the inferior vena cava is 1.8%. Complications involving the inferior vena cava are associated with high morbidity and mortality [1].

Suprahepatic inferior vena cava (SHIVC) anastomotic stenosis occurred in 1.1% of patients after OLT. Stenosis may occur in the early postoperative period or as long as 4.5 years later. Stenosis identified in the early postoperative period is associated with caval torsion or kinking. Clinical manifestations are dependent upon the severity of the stenosis [2–4].

The cause of pulmonary hypertension following OLT is unknown. The severe occlusion to hepatic venous drainage leads to recurrence of portal hypertension (POH) and increased resistance to pulmonary blood flow. The restricted flow through the pulmonary arterial circulation results in increase of pulmonary vascular resistance (PVR) and right heart failure [1,5–7].

In the current case report, we describe a patient who developed stricture of the SHIVC anastomosis and pulmonary arterial hypertension (PAH) after OLT.

Case Report

A 54-year-old woman underwent OLT 4 years ago for end-stage liver disease caused by hepatitis C virus. Her medical history was significant – she smoked daily for 38 years, and had arterial hypertension for 9 years and hypothyroidism for 4 years. Before transplantation, lung function test results were in the normal range. She also had a transthoracic Doppler echocardiogram, which revealed normal left and right ventricular size and function. Pulmonary hemodynamic parameters assessed by pulmonary artery catheterization at the time of OLT were normal. The donor was a 25-year-old man with head trauma, hemodynamically stable, normal anatomy, and normal liver functions test results. The cold ischemia time was 6 hours. The liver was grafted with a “piggyback” technique, preserving the native vena cava by doing a hepatocaval anastomosis.

Her postoperative course was complicated by an early episode of pneumonia from which she recovered and was discharged. She developed abdominal pain 24 days later. The patient was readmitted to the hospital and was surgically treated for perforated diverticular colonic disease. She recovered uneventfully from the surgery and was discharged.

Twenty months after transplantation, she developed fatigue and progressive ascites with normal findings on hepatic Doppler sonogram. She was treated medically with dietary sodium restriction, spironolactone, and furosemide to control the ascites. After 3 months, the Doppler sonogram was repeated to reevaluate the hepatic vessels, which demonstrated narrowing of the lumen of the inferior vena cava at the suprahepatic anastomosis, POH, hepatomegaly, and ascites. Obstruction of the SHIVC was presumed and this diagnosis was confirmed by CT angiogram.

Upon admission to the university Hospital Civil de Guadalajara “Fray Antonio Alcalde”, physical examination revealed the following findings: hepatomegaly, lower limb edema, and ascites. Laboratory values showed impaired renal function (serum creatinine 1.4 mg/dL and estimate creatinine clearance of 41 ml/min). Her liver function tests were: 1.3 mg/dL total bilirubin, 229 IU/L gamma-glutamyl transpeptidase, 280 IU/L alkaline phosphatase, 10 IU/L alanine aminotransferase, 19 IU/L aspartate aminotransferase, 13.4 s prothrombin time and 3.3 g/dL albumin. She was receiving immunosuppressive therapy (tacrolimus, mycophenolate mofetil, and prednisone), antihypertensive drugs (lisinopril and amlodipine), and thyroid hormone replacement therapy (thyroxine), as well as bumetanide and allopurinol.

Surgical correction of the SHIVC anastomotic stricture was performed. Anesthesia was induced with midazolam, fentanyl, atracurium, and thiopental, and maintained with isoflurane, fentanyl, and atracurium. The graft appeared severely congested and 4 L of ascites was found. The degree of stricture was 95% in the anastomotic site. The lumen measured 0.5mm in diameter and the obstruction was caused by the presence of a fibrotic ring of connective tissue involving the suture line. The graft was vascularly excluded by clamping the hilum and the infra-hepatic and suprahepatic vena cava, and the hepatocaval anastomosis was dismantled for direct exploration. The liver was perfused with Histidine-Tryptophan-Ketoglutarate preservation solution at 4°C in a retrograde fashion. The hepatocaval anastomosis was reconstructed by an end-to-end venous anastomosis. Clamps were released and the liver recovered normal aspects with no congestion. The ischemic time was 47 min. During intraoperative monitoring, her blood pressure fell to 80/40 mmHg and norepinephrine was begun. At this time, central venous pressure was 9 mmHg and 100% of oxygen was administered. At the end of surgery, the patient was hemodynamically stable. The patient was transfused 5 U of fresh frozen plasma. The total operative time was 6 h. The patient was extubated and norepinephrine was discontinued 19 h after surgery. The hepatic Doppler sonogram after surgery demonstrated normal flow.

The patient was transferred to the intensive care unit, where her postoperative course was complicated. On postoperative

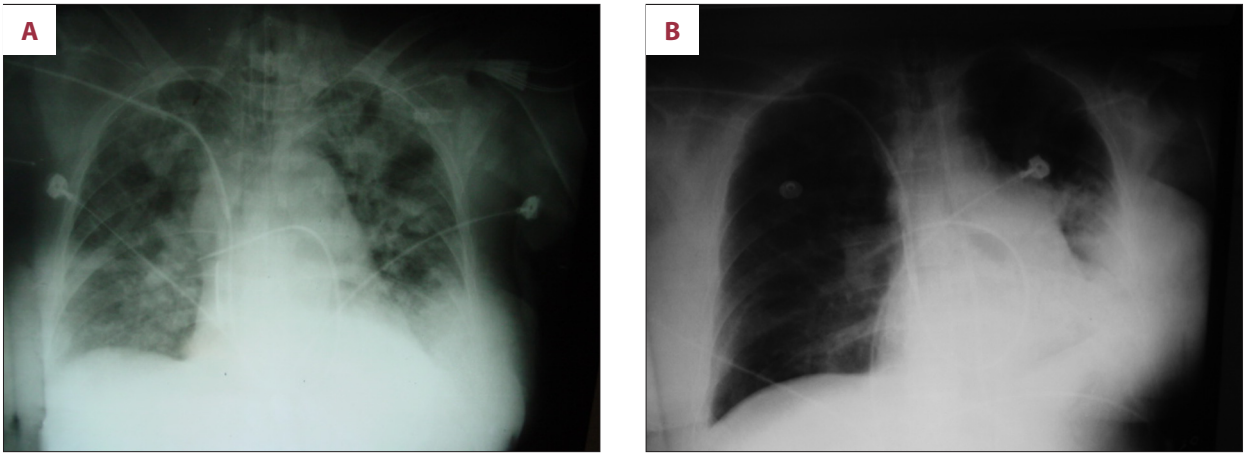

Figure 1. (**A**) Chest radiograph on postoperative day 3 showing diffuse bilateral infiltrates. (**B**) Chest radiograph on postoperative day 5 showing a nearly clear lung fields.

day (POD) 1, her condition started to deteriorate and she developed progressive dyspnea. An arterial blood-gas determination revealed a P_{O2} of 60 mm Hg, P_{CO2} of 38 mm Hg, pH of 7.45, Sa_{O2} of 92%, and lactate of 1.3 mmol/L. The mixed venous oxygen saturation (Sv_{O2}) was 66%, with a ratio of arterial partial pressure to fraction of inspired oxygen (P_{aO2}/F_{IO2}) of 150 mmHg, and arterial oxygen content (Ca_{O2}) of 12.95 O_2/dL. Oxygen was begun by facemask at 0.5 L/min. However, she failed to improve and noninvasive positive pressure ventilation was started. Furosemide was begun at a dose of 80 mg/day.

On POD 2, despite aggressive noninvasive positive pressure ventilation support, she required elective endotracheal intubation for refractory hypoxemia and she was connected to the ventilator with an assist/control mode, F_{IO2} of 1 L/min and positive end-expiratory pressure of 12 cm H_2O. A subsequent arterial blood-gas determination revealed a P_{O2} of 57 mmHg, P_{CO2} of 60 mm Hg, pH of 7.29, Sa_{O2} of 86%, and lactate of 1.1 mmol/L. The SvO_2 was 52% and calculated P_{aO2}/F_{IO2} ratio of 57 mmHg, Ca_{O2} of 12.46 O_2/dL, alveolar-arterial oxygen pressure difference ($PA\text{-}a_{O2}$) of 457 mmHg, and intrapulmonary shunt fraction (Q_S/Q_T) of 24.8%. Her chest radiograph showed diffuse bilateral infiltrates consistent with pulmonary edema (Figure 1A). The severity of organ dysfunction was assessed using a Sequential Organ Failure Assessment score and this was calculated to be a score of 9. Procalcitonin was determined at 0.82 ng/ml. Initial empiric antimicrobial therapy with piperacillin/tazobactam, linezolid, caspofungin, and oseltamivir was begun. Blood pressure fell to 87/54 mmHg and norepinephrine was required.

Catheterization was performed using a triple-lumen, balloon-tipped thermodilution catheter on POD 3 and showed mild pulmonary hypertension and elevated PVR. The mean pulmonary arterial pressure was 29 mmHg, PVR of 401 dynes-s/cm^5, cardiac output of 4.7 L/min, pulmonary artery occlusion pressure of 6 mmHg, central venous pressure of 11 mmHg, cardiac index of 2.6 L, and transpulmonary gradient of 23 mmHg. Dobutamine was begun at a dose of 5 mcg/kg/min.

A transthoracic Doppler echocardiogram showed an enlarged right ventricular, right ventricular systolic pressure of 50 mm Hg, and left ventricular ejection fraction of 70%. After these findings, oral sildenafil was then started at 50 mg twice a day. On POD 5, the chest film had cleared (Figure 1B) and ventilator support was diminished gradually. The patient continued with assist/control mode, F_{IO2} of 0.5 L/min, and positive end-expiratory pressure of 8 cm H_2O.

Right heart catheterization was conducted for 7 days. Repeated hemodynamic measurement showed mean pulmonary arterial pressure mean of 33±4 mmHg with a range of 29–39 mmHg, PVR mean of 316±26 with a range of 253–472 dynes-s/cm^5, pulmonary artery occlusion pressure mean of 13±4 mmHg with a range of 6–18 mmHg, cardiac output mean of 6±0.6 L/min with a range of 4.7–6.5, and cardiac index mean of 3±0.5 with a range of 2–3.6 L. Before the catheter was removed, a decrease in PVR and increase in cardiac index was observed.

Pulmonary embolism diagnosis was excluded by chest CT angiogram, which showed dilated pulmonary arteries and a right pleural effusion. Her thyroid function was in the normal range.

After 6 days of mechanical ventilation, ventilator-associated pneumonia was suspected when she developed new pulmonary infiltrates involving the left lower lobe on chest radiograph, purulent tracheobronchial secretions, leukocytosis, and procalcitonin of 0.61 ng/ml. Bronchoscopy was performed with a bronchoalveolar lavage. The specimen obtained was examined for bacterial, fungi, acid-fast bacilli, and *Pneumocystis jirovecii*. Piperacillin/tazobactam was discontinued and cefepime and trimethoprim/sulfamethoxazole were given. The direct

immunofluorescent stains for *Pneumocystis jirovecii* and Ziehl-Neelsen stains were negative. Cultures yielded *Acinetobacter calcoaceticus*. A hepatic Doppler sonogram result was normal.

The patient was extubated on POD 11 with a decrease in norepinephrine and dobutamine requirement, leading to its discontinuation.

On POD 12, a thoracentesis was performed, revealing right pleural effusion of 400 ml. Pleural fluid was examined with cloudy appearance, pH 8.2, protein 1.9 g/dL, glucose 166 mg/dL, lactate dehydrogenase 346 U/L, ratio of pleural fluid protein to serum 0.52, leukocytes 20 per low-power field (100×) with polymorphonuclear neutrophils of 81%, and mononuclear cells of 19%. Direct immunofluorescent stains for *Pneumocystis jirovecii* were positive. Bacterial and fungal cultures were negative.

She was discharged home on POD 15, and has remained well for 1 year after discharge. A transthoracic Doppler echocardiogram after 2 months was normal and sildenafil was discontinued.

Discussion

Vascular complications after OLT include occlusion or stenosis at the sites of anastomosis [3]. Most frequently, vascular stenosis is related to arterial anastomosis [8]. The incidence of clinically unsuspected stenosis at hepatic arteriography and portal venography on routine follow-up 2 months and 1 year after OLT occurred in 9% and 5% (hepatic artery) and in 3% and 5% (portal vein), respectively [9]. Vascular complications following to the technique of "piggyback" OLT has shown a low risk of venous outflow obstruction. Late hepatic vein obstruction is a rare complication, affecting less than 3% of OLT patients [10,11]. A contributing factor in the development of stenosis at the SHIVC anastomosis includes patients undergoing a retransplantation by excessive fibrous tissue [2,12].

Symptoms in the patient developed gradually over time. Clinical manifestations of SHIVC anastomotic stenosis are dependent upon their severity and have been reported to cause: lower limb edema, renal failure, hypotension, ascites, hepatic functional abnormalities, hepatomegaly, recurrent pulmonary embolism, recurrence of POH, and severe esophageal varices [1–3].

Therapeutic options for stenosis of the SHIVC anastomosis after OLT include percutaneous transluminal angioplasty, with or without stent implantation, surgical reconstruction of the venous anastomosis, and retransplantation [1–4,12].

Acute cor pulmonale after venous decompression of SHIVC with preexisting portopulmonary hypertension (POPH) is a severe complication. Sudden increased return of venous blood into the heart may cause or precipitate right heart failure. The differential diagnosis includes massive pulmonary embolism and acute respiratory distress syndrome, because they are the most common clinical conditions associated with acute cor pulmonale [6].

We suggest that reperfusion pulmonary edema could be another diagnosis to consider. Reperfusion pulmonary edema is a form of lung injury and it is the most frequent complication after pulmonary endarterectomy [13]. The physiologic changes that occur following pulmonary endarterectomy include a dramatic reduction in right ventricular afterload and redistribution of pulmonary blood flow. The most common postoperative hemodynamic profile includes an immediate and sustained reduction of pulmonary artery pressure, associated with marked increase in cardiac output and normalization of PVR. Less common are increases in cardiac output associated with improvement, but not normalization, of pulmonary artery pressures and PVR and significant levels of pulmonary hypertension that persist in the postoperative period [14].

To our knowledge, stenosis of the SHIVC anastomosis and POPH after OLT has not been described previously. There was no clinical suspicion of PAH at the time the patient´s admission to the hospital. However, she was receiving calcium channel blockers, which may have effected the PAH. POPH is defined as the development of PAH complicated by POH, with or without advanced hepatic disease. POPH is defined by hemodynamic criteria and is determined via catheterization. Staging of severity of POPH is based on mean pulmonary arterial pressure using the diagnostic criteria proposed by the European Respiratory Society-European Association for the Study of the Liver [15].

The incidence of POPH in patients with end-stage liver disease is high, and is estimated to occur in up to 65% in patients assessed for liver transplantation with right ventricular systolic pressure >50 mm Hg and right heart catheterization [5]. Patients with moderate or severe POPH, who are able to reduce their mean pulmonary arterial pressure to <35 mm Hg with vasodilation therapy, have excellent survival rates following liver transplantation. POPH usually improves or resolves relatively quickly after liver transplantation, but occasionally requires continuation of vasodilation therapy for several months [16].

The pathogenesis of pulmonary vascular disorders after OLT remains uncertain. PAH after OLT has been recognized in 4 clinical settings: **1**. Patients with hepatopulmonary syndrome prior to OLT (in 2 patients, the hepatopulmonary syndrome resolved spontaneously after OLT, followed by onset of pulmonary hypertension) [17]; **2**. Patients with recurrent cirrhosis and POH; **3**. Patients with POPH prior to OLT (1 patient with POPH successfully underwent OLT 14 months after beginning sildenafil. This patient had worsening of PAH 6 months posttransplant, necessitating epoprostenol. PAH was exacerbated after OLT)

[18]; and **4**. Isolated PAH [19]. Through managing this case, we found that recurrent POH caused by vascular complications is another cause of PAH after OLT.

Nonetheless, diseases associated with PAH should be considered in the evaluation of every patient with PAH that develops after OLT [7]. Our patient could have another possible cause of PAH, such as thyroid disease, pulmonary vascular changes caused by smoking, or infection by *Pneumocystis jirovecii*. Experimental models have demonstrated that pulmonary hypertension is a sequela of *Pneumocystis* pneumonia. The immune response to an infectious disease pathogen when perturbed and prolonged can lead to later development of pulmonary hypertension [20].

Cause of liver disease and severity of hepatic dysfunction have no relationship to the severity of POPH [5,21]. However, chronic hepatitis C virus infection is associated with multiple extrahepatic manifestations, including its primary effects in lung disease [22].

The clinical response of a patient with POPH treated with sildenafil (a phosphodiesterase-5 inhibitor) supports that sildenafil may be an effective therapy for POPH with preserved cardiac function [18,23].

Conclusions

Patients with stenosis of the SHIVC and PAH my have a high risk for cardiopulmonary-related mortality. Further trials are needed to define all causes that predispose them to PAH after OLT. Sildenafil is an effective therapy for PAH after POH by vascular complications.

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