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Protein-losing Enteropathy Due to Inferior Vena Cava Stenosis in a Liver Transplant Recipient

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INTRODUCTION

Inferior vena cava (IVC) stenosis is an uncommon complication of liver transplantation (LT) and is seen in <3% of all LTs. We describe a novel presentation of IVC stenosis in a liver transplant recipient resulting in protein-losing enteropathy (PLE) and treated successfully with stent placement across the stenosis with subsequent resolution of symptoms.

CASE REPORT

A 27-y-old male LT recipient was seen in the outpatient clinic for evaluation of diarrhea and anasarca. He first reported diarrhea about 1 y after LT, and at that time, it was mild and responded to loperamide. At this visit, he reported 4–5 nonbloody, watery stools, not responsive to loperamide. The patient's symptoms were associated with generalized weakness and marked bilateral lower extremity edema extending to the sacrum. He denied any history of nausea, vomiting, abdominal pain, tenesmus, fevers, sweats, or chills.

His medical history is significant for an orthotopic, deceased donor liver transplant at the age of 12 mo for biliary atresia. Twenty-three years after his LT, following an episode of medication noncompliance, he developed moderately severe acute cellular rejection and mild chronic rejection, which was

treated with high dose corticosteroids. He, however, continued to progress and was hospitalized with liver failure and Gram-negative bacteremia. He ultimately underwent a second deceased donor liver transplant using a piggyback technique. His last hospital stay was complicated by colonic perforation requiring a right hemicolectomy.

At the time of his clinic visit, the patient's medications included tacrolimus, coumadin, loperamide, mycophenolic acid, ursodeoxycholic acid, and omeprazole. On physical examination, mild abdominal distension was present in addition to severe bilateral lower extremity and sacral edema. The remainder of the patient's physical examination was normal.

The patient's initial laboratory evaluation showed a serum creatinine of 1.45 mg% and a serum albumin of 1.6 g%. Liver tests and a complete blood count were normal. Urinalysis did not show proteinuria. An echocardiogram showed normal left and right ventricular function and no valvular abnormalities. An ultrasound with Doppler examination of the transplanted liver showed no evidence of vascular abnormalities, although a small amount of ascites was noted; this was not amenable to diagnostic paracentesis. Microbiological evaluation of stool yielded a positive polymerase chain reaction assay for *Clostridioides difficile*. The patient was started on oral vancomycin and later fidaxomicin for recurrent infection.

At a follow-up clinic visit, the patient continued to report loose stools, albeit decreased frequency compared to his prior visit, and anasarca persisted. Repeat laboratory evaluation included a negative polymerase chain reaction assay for *C. difficile* and microbiologic enteric panel was also negative. The patient's repeat serum albumin was 2.1 g%, and he was receiving intermittent albumin infusions; serum creatinine was 1.3 mg%. His hemoglobin concentration was 8.7 g%. Because of ongoing diarrhea, mycophenolate mofetil was discontinued and azathioprine was added.

Because of the severe hypoalbuminemia, without an obvious source of albumin loss, a 24-h stool alpha-1-antitrypsin clearance was obtained and resulted at >58 mL/d, strongly suggesting PLE. Magnetic resonance enterography was obtained, showing normal small and large bowel without evidence of inflammation. The patient underwent upper endoscopy with random biopsies, which were negative for celiac disease or posttransplant lymphoproliferative disorder. Colonoscopy showed a healthy ileocolonic anastomosis with normal colon, rectal, and ileal mucosa. Colonic biopsies revealed mild edema but no evidence of inflammation or posttransplant lymphoproliferative disorder.

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The patient underwent a transjugular liver biopsy with measurement of portal pressures to evaluate his ascites. The portosystemic gradient was ~15 mmHg with venography suggesting a narrowing near the cavoatrial junction. Liver histology showed sinusoidal dilatation but no inflammation or fibrosis (Figure 1). Computed tomographic angiogram with 3D reconstruction showed short segment stenosis located at the original IVC anastomosis (Figure 2).

The patient initially underwent balloon venoplasty, which failed due to significant IVC recoil. Venoplasty with placement of a 20mm Gianturco stent across the area of severe stenosis was then performed: this was dilated to 18mm with a decrease in portosystemic gradient to 6–7 mmHg. Repeat venocavagram a few days later showed a zero-pressure gradient across the stent (Figure 3).

The patient's symptoms rapidly improved with complete cessation of diarrhea, as well as subsequent resolution of ascites and leg swelling, with complete normalization of serum albumin concentration. Follow-up imaging at 6 mo and at 1-y poststent placement showed a widely patent stent with no evidence of recurrent stenosis. Two years after presentation, the patient continues to do well with no recurrence of symptoms and good quality of life.

DISCUSSION

IVC stenosis is an unusual complication of LT, seen in <3% of all LTs. It has become even less common in recent years with the use of the modified-piggyback with 3-hepatic vein technique for orthotopic LTs.^{1,2}

The clinical presentation of IVC stenosis is highly variable. Patients with IVC stenosis post-LT may present early or late after transplant with the timing of presentation ranging from d 0 to d 797 post-LT.³ Furthermore, the etiology of IVC stenosis can influence the timing of presentation. IVC stenosis in the early posttransplant period is usually mechanical, related to donor-recipient IVC diameter mismatch with kinking, thrombosis, or hematoma formation, whereas chronic intimal thickening and fibrosis are usually the main causes in later cases.¹ The exact etiology of IVC stenosis in our patient is unclear. An MRI obtained before his retransplantation showed relative atrophy of his left hepatic lobe. It is, therefore, quite plausible that some caval twisting may have played a role in the pathologic process. Regarding symptoms, early presentations of IVC stenosis can present with high abdominal drain output, and in a few cases, abnormal liver enzymes. Later presenting cases may manifest with findings of portal hypertension such as edema, ascites, and pleural effusion.³ Our patient also had mild renal dysfunction that was attributed to hypovolemia and prerenal injury from gastrointestinal fluid loss but may have also had a component of renal congestion from IVC stenosis.

This is the first published adult case of IVC stenosis causing PLE. PLE is a clinical syndrome defined by loss of albumin from the gastrointestinal tract that is characterized by hypoalbuminemia and edema. PLE is typically related to a variety of malignant, infectious, and inflammatory diseases.⁴ Diagnosis involves confirmation of protein loss in the stool as indicated by a decreased 24-h stool alpha-1-antitrypsin clearance followed by thorough imaging and endoscopic

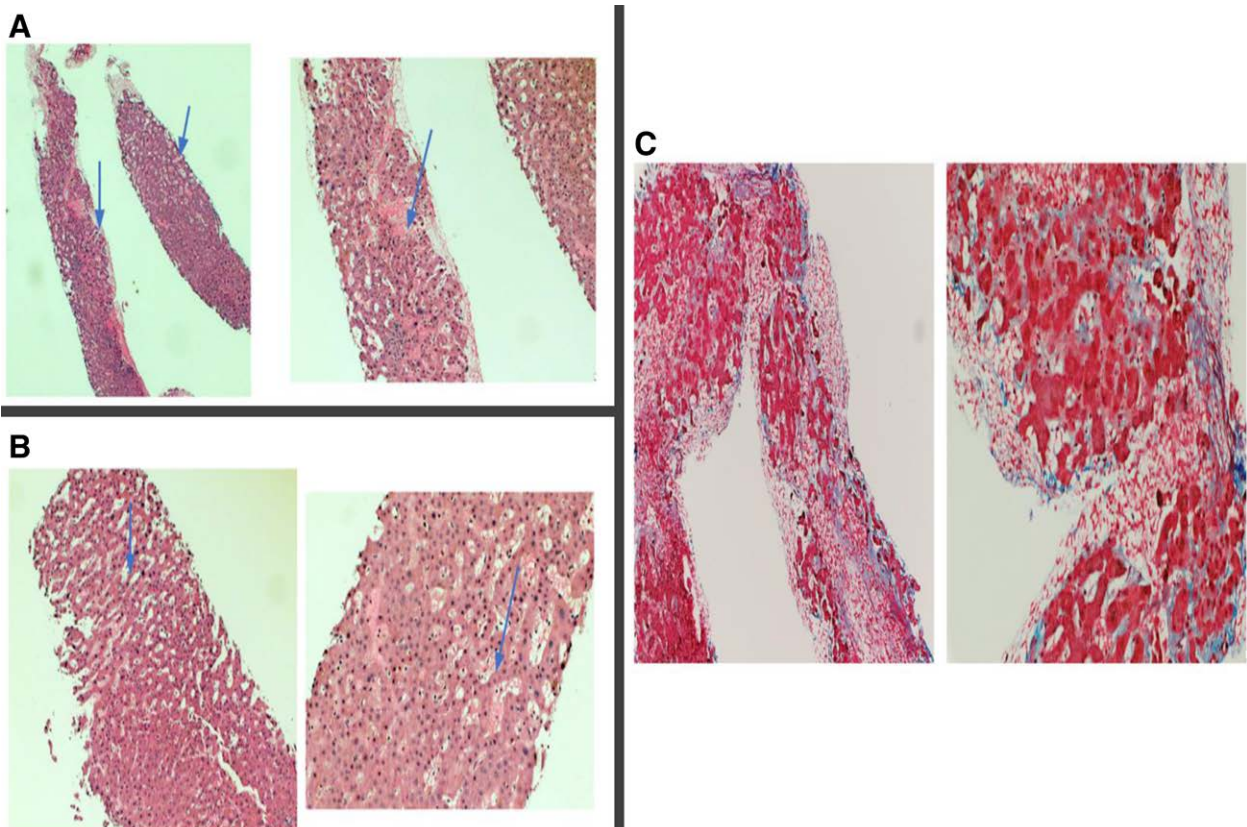


FIGURE 1. Transjugular liver biopsy findings. Liver biopsy with hematoxylin and eosin staining showing sinusoidal dilatation associated with hepatocellular atrophy (blue arrows) and no evidence of acute or chronic rejection (A and B); and trichrome stain showing no significant fibrosis (C).

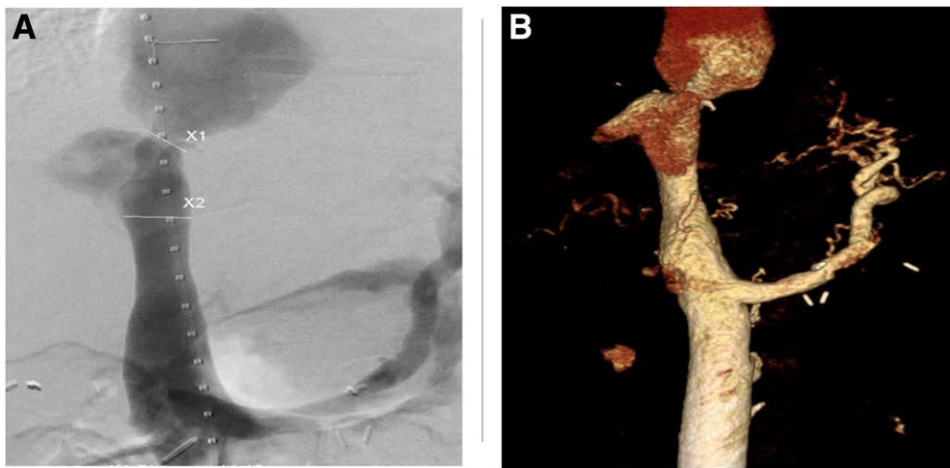


FIGURE 2. Diagnostic radiology. Inferior vena cava (IVC) stenosis demonstrated on venocavagram (A) and computed tomography with 3D reconstruction (B).



FIGURE 3. Interventional radiology images. Venocavagram before (A) and after stent placement (B) showing improvement of stenotic segment (black arrows).

evaluation to determine etiology.^{4,5} In our patient's case, IVC stenosis, presumably related to his first liver transplant, may have resulted in portal hypertension causing bowel congestion and leakage of albumin into the bowel lumen. A slow progression of the patient's IVC stenosis may account for the development of bowel symptoms in our patient, as compared to more typical presentations of portal hypertension. A similar pathophysiology has been observed in patients with congenital heart disease who develop PLE after a Fontan operation, which often presents with a similarly insidious onset.⁶

IVC stenosis can be treated with balloon venoplasty and is typically more effective in cases with an early presentation. Patency following venoplasty is often not durable in cases of chronic IVC stenosis because of the inherent elasticity of the IVC resulting in recoil of the fibrotic tissue, as was seen in our patient. The role of balloon venoplasty is further limited due to reduced efficacy in tortuous grafts and the potential for anastomotic rupture.⁷ Despite these issues, balloon venoplasty may be deployed as a first-time treatment as part of a less invasive "step-up" approach before proceeding to other modalities.

In later presenting cases of IVC stenosis, where there is significant intimal thickening and fibrosis, or in patients who fail balloon venoplasty, stenting of the IVC can be done. IVC stent placement for this purpose was first described in 1993 by Berger et al,⁸ and is now the preferred treatment. Multiple studies, including a large meta-analysis of 17 studies and 73 patients, have documented significant efficacy with resolution of presenting symptoms (termed clinical success) in 96%–100% of patients.^{9–11} IVC stent placement is also very durable with a primary patency rate of >80% after a median follow-up of 4.5 y as described in a recent retrospective series of 29 patients.⁹ Other studies have documented a similar 85%–100% primary patency after 1- to 2-y follow-up.^{3,12} Despite its clear efficacy, IVC stenting has been associated with multiple complications, including stent migration and restenosis, as some of the most commonly documented adverse effects.^{13,14}

In summary, IVC stenosis is an unusual complication of LT with highly variable clinical symptoms on presentation. We report a first adult case of PLE related to IVC stenosis after LT with full resolution of symptoms following stent placement. PLE should be considered in liver transplant recipients

presenting with persistent diarrhea, potentially as a result of a vascular complication.

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