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# Rapid Development of Post–Liver Transplantation Nodular Regenerative Hyperplasia and Portal Hypertension After Perfusion Pump Use: A Case Series

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On September 28, 2021, the TransMedics Organ Care System (OCS) became the first normothermic perfusion pump to receive Food and Drug Administration approval in liver transplantation (LT). Since then, perfusion pump use has spread widely because it significantly extends ex vivo organ viability time compared with traditional static cold storage.[1] We present a case series of 4 patients who rapidly developed biopsy-proven nodular regenerative hyperplasia (NRH) and portal hypertension after LT with perfusion pump utilization at a single institution in 2022–2024. Pretransplant biopsies for all cases are presented in the case figures. TransMedics OCS mean pump parameters for all cases are included in Table 1.

## CASE 1

Patient 1 is a 56-y-old man with a history of alcohol-associated liver disease and normal baseline renal function whose deceased brain donor (DBD) was a 65-y-old woman with a body mass index (BMI) of 26.8 kg/m$^2$ and a history of chronic hepatitis C (nucleic acid test$^-$) who died after a cerebrovascular accidence. The donor organ was placed on the TransMedics OCS for 7 h and 38 min. The patient experienced a brief episode of hypotension intraoperatively during this successful whole liver, duct-to-duct transplantation. Relevant laboratory tests on postoperative day (POD) 1 included aspartate aminotransferase (AST) 143 U/L, alanine transaminase (ALT) 80 U/L, alkaline phosphatase (ALP) 46 IU/L, total bilirubin (tbili) 4.7 mg/dL, blood urea nitrogen (BUN) 41 mg/dL, creatinine (Cr) 1.7 mg/dL, platelets 107/L, and international normalized ratio (INR) 2.2. He was started on tacrolimus, mycophenolate, and prednisone post-LT and remained admitted after his transplantation because of uptrending bilirubin and ALP. On POD 9, the patient developed an acute kidney injury (AKI) with Cr 2.2 mg/dL and BUN 43 mg/dL. Post-LT duplex ultrasound demonstrated normal hepatic vasculature flow. The patient progressively developed clinically significant portal hypertension (CSPH), with ascites and hepatic hydrothorax. Transjugular biopsy (TJB) 4 wk post-LT showed a portosystemic gradient of 18 mm Hg, a right atrium (RA) pressure of 12 mm Hg, and a free hepatic vein pressure (HVP) of 16 mm Hg; pathology did not show signs of rejection but did show NRH (Figure 1). The patient had an extensive workup for secondary causes of CSPH, including a normal cardiac workup, normal inferior vena cava (IVC) venogram, and no evidence of splenic steal on angiogram. A splenic artery embolization was performed, given prior data that suggest this may improve post-LT portal pressure gradients.[2] The patient became progressively oliguric, requiring escalating diuretic doses and treatment for hepatorenal syndrome. Renal replacement therapy (RRT) was initiated at 7 wk post-LT for volume management, leading to clinical improvement. RRT was stopped by 13 wk post-LT with resolution of portal hypertension symptoms without continued need for diuretics. Over the next year, his course was complicated by anastomotic biliary strictures requiring multiple endoscopic retrograde cholangiopancreatography with stent placements without recurrence of portal hypertension symptoms. Twelve months post–initial LT, the patient underwent repeat LT. Explant pathology of the allograft liver showed NRH.

## CASE 2

Patient 2 is a 50-y-old man with a history of metabolic dysfunction-associated steatotic liver disease with normal baseline renal function whose DBD was a 59-y-old man with a BMI

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**TABLE 1.**
**Mean TransMedics OCS pump parameters**

| Patient case | PF, L/min | Hepatic artery flow, L/min | Portal vein flow, L/min | Mean hepatic artery pressure, mm Hg | Systolic hepatic artery pressure mean, mm Hg | Diastolic hepatic artery pressure mean, mm Hg | Mean portal vein pressure, mm Hg | Perfusate temperature, C | Perfusate venous saturation, % | Perfusate hematocrit, % | SDS bile salt, mL/h | Arterial lactate initial OCS | Arterial lactate final OCS | Bile |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 1.98 | 0.48 | 1.5 | 50 | 74 | 28 | 7 | 33.8 | 98 | 27 | 4 | 5.31 | 0.89 | 15 |
| 2 | 1.87 | 0.5 | 1.37 | 44 | 70 | 23 | 3 | 33.8 | 96 | 36 | 3 | 9.69 | 0.3 | 75 |
| 3 | 1.88 | 0.58 | 1.3 | 48 | 77 | 24 | 3 | 33.7 | 96 | 23 | 3 | 5.15 | 0.86 | 30 |
| 4 | 1.75 | 0.34 | 1.41 | 53 | 72 | 35 | 7 | 33.7 | 97 | 32 | 3 | 6.65 | 2.53 | 25 |

OCS, Organ Care System; PF, pump flow (total flow of combined portal vein + hepatic artery); SDS, substrate delivery system.

of 43.4 who died from cardiac arrest. The donor organ was placed on the TransMedics OCS for 18 h and 29 min. There were no intraoperative episodes of hypotension in this successful duct-to-duct LT with a standard caval replacement technique. POD 1 laboratory tests showed BUN 24 mg/dL, Cr 1.1 mg/dL, AST 753 U/L, ALT 598 U/L, tbili 1.5 mg/dL, platelets 55/L, and INR 1.7. The patient was started on tacrolimus, mycophenolate, and prednisone and discharged on POD 10. Within 3 wk of transplantation, the patient developed worsening ascites and lower extremity edema. He was readmitted for volume overload and found to have an AKI with BUN 73 mg/dL and Cr 1.9 mg/dL. Liver duplex ultrasound showed normal portal vein and hepatic artery flow. TJB at 4 wk post-LT revealed a portosystemic gradient of 11 mm Hg, with a free HVP of 18 mm Hg and RA pressure of 25 mm Hg; the tissue sample was small limiting analysis. Right heart catheterization showed elevated filling pressures (RA 14 mm Hg) and preserved cardiac index. He was trialed on diuretics as well as dopamine but did not clinically respond. The hepatic venogram did not show IVC narrowing. Repeat TJB 6 wk post-LT showed an increased portosystemic gradient to 14 mm Hg, with pathology notable for NRH (Figure 2). Patient 2 underwent an extensive workup for secondary causes of portal hypertension, notable for possible preferential flow toward the splenic artery, leading this patient to undergo a splenic artery embolization. He started RRT 7 wk post-LT for aggressive volume management with clinical improvement and stopped RRT within 10 wk post-LT. His maintenance diuretic therapy was weaned and eventually stopped. Repeat TJB at 11 wk post-LT demonstrated a portosystemic pressure gradient of 13 mm Hg with a free HVP of 5 mm Hg. Pathology remained suggestive of NRH.

## CASE 3

Patient 3 is a 53-y-old woman with a history of metabolic dysfunction-associated steatotic liver disease and normal baseline renal function whose DBD was a 57-y-old man with a BMI of 28.5 and a history of alcohol use. The donor organ was placed on the TransMedics OCS for 12 h and 13 min. The patient underwent successful duct-to-duct LT with the standard caval replacement technique. Intraoperatively, there were no prolonged episodes of hypotension. POD 1 laboratory tests were notable for BUN 26 mg/dL, Cr 1.0 mg/dL, AST 1970 U/L, ALT 650 U/L, tbili 2.9 mg/dL, platelets 60/L, and INR 1.8. The patient was started on tacrolimus, mycophenolate, and prednisone post-LT and discharged on POD 6. The patient was seen in the clinic on POD 10 where she had increasing ascites and lower extremity edema and was readmitted for diuretics and paracentesis. Doppler ultrasound showed main hepatic artery stenosis at the anastomosis site, and TJB and venogram showed narrowing at the IVC superior anastomosis with a 9-mm Hg gradient across and an 18-mm Hg portal/RA pressure gradient. Pathology showed moderate T cell–mediated allograft rejection, which was treated. At 6 wk post-LT, she underwent IVC angioplasty with a reduction of the gradient across the anastomosis to 3 mm Hg. Repeat TJB showed a 16-mm Hg portosystemic gradient, and pathology showed treated acute cellular rejection with NRH (Figure 3). Because of persistent AKI and concern for hepatorenal physiology, the patient was started on RRT. She had a prolonged admission and was discharged at 10 wk post-LT with RRT stopped 12 wk post-LT with continuation of maintenance diuretics.

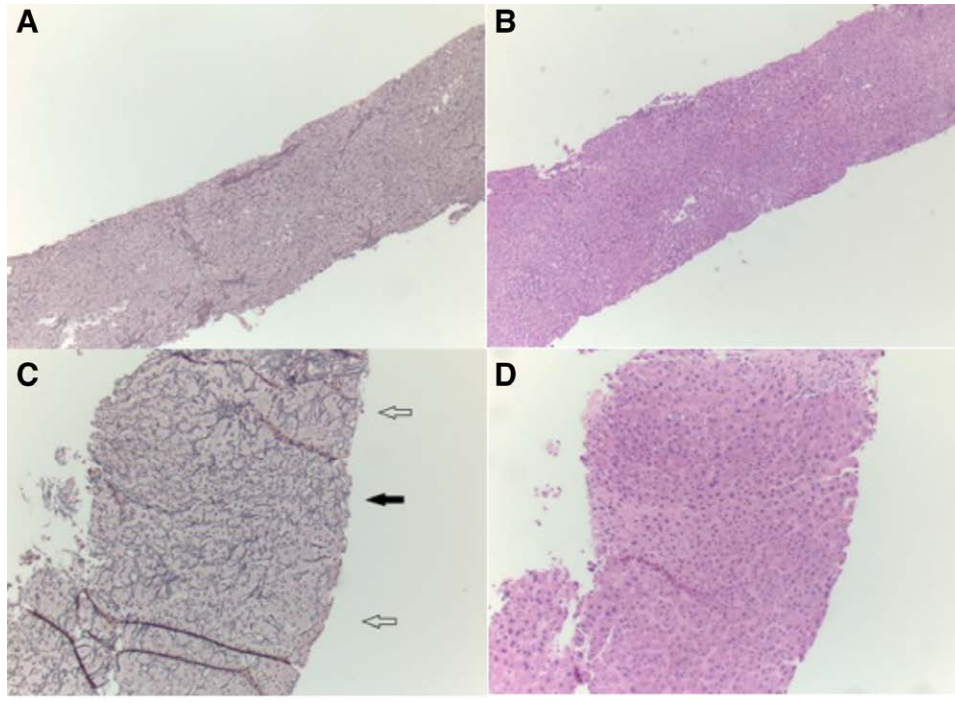


**FIGURE 1.** Pre/posttransplant biopsies for case 1. Pre- and posttransplant biopsies for case 1. A, Biopsy of pretransplant donor liver without significant pathology findings (reticulin, ×100). B, Biopsy of pretransplant donor in H&E stain (×100) without significant pathology findings. C, Biopsy of posttransplant liver showing alternately expanded and compressed hepatic plates, suggestive of NRH (reticulin, ×100). D, Biopsy of posttransplant liver in H&E stain (×100) showing evidence of NRH. H&E, hematoxylin and eosin; NRH, nodular regenerative hyperplasia.

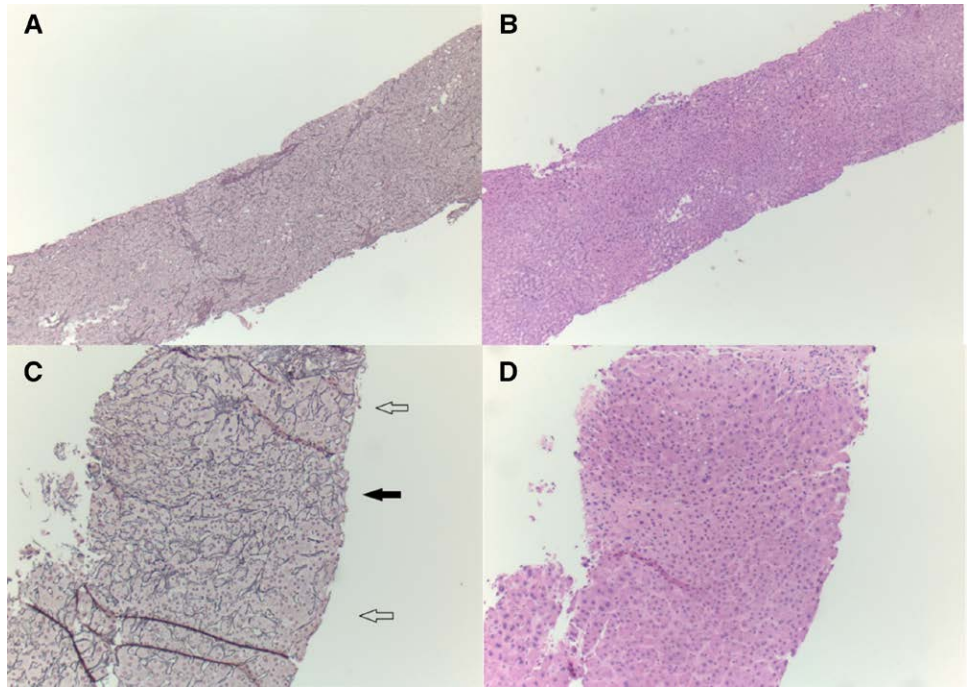


**FIGURE 2.** Pre/Posttransplant biopsies for case 2. Pre- and posttransplant biopsies for case 2. A, Biopsy of pretransplant donor liver without significant pathology findings (reticulin, ×40). B, Biopsy of pretransplant donor in H&E stain (×40) without significant pathology findings. C, Posttransplant liver biopsy highlighting the key feature of NRH with alternately expanded (white arrows) and compressed (black arrow) hepatic plates (Reticulin, ×100). D, Biopsy of posttransplant liver in H&E stain (×100) showing evidence of NRH. H&E, hematoxylin and eosin; NRH, nodular regenerative hyperplasia.

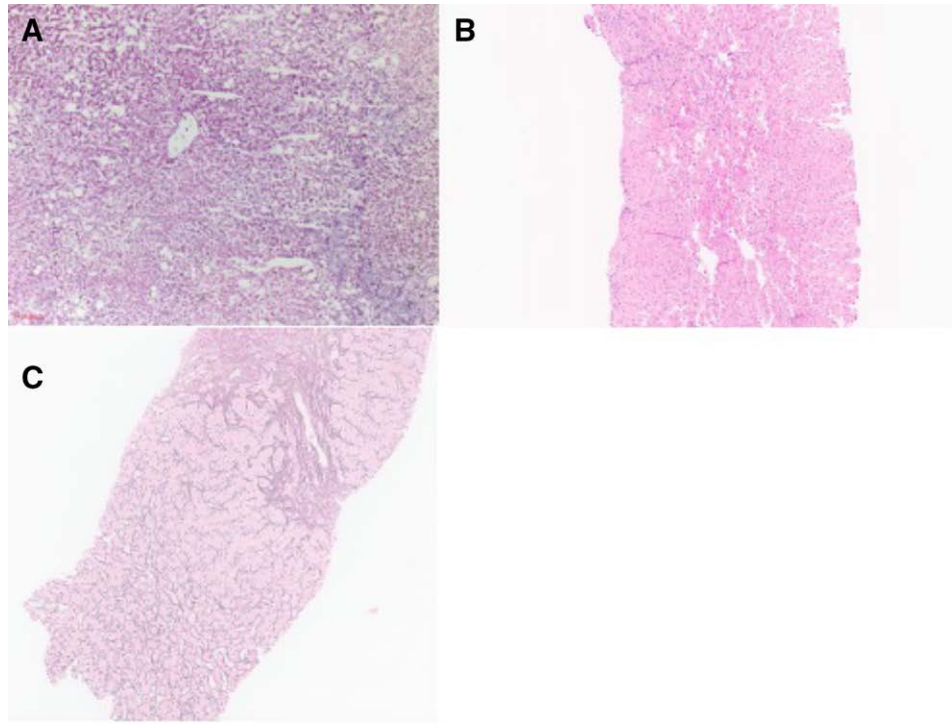


**FIGURE 3.** Pre/posttransplant biopsies for case 3. Pre- and posttransplant biopsies for case 3. A, Biopsy of pretransplant donor liver without significant pathology findings (H&E, ×100). No reticulin stains were performed. B, Biopsy of posttransplant liver in H&E stain (×100) showing evidence of NRH. C, Reticulin stain of posttransplant liver biopsy shows alternately expanded and compressed hepatic plates, suggestive of NRH (reticulin, ×100). H&E, hematoxylin and eosin; NRH, nodular regenerative hyperplasia.

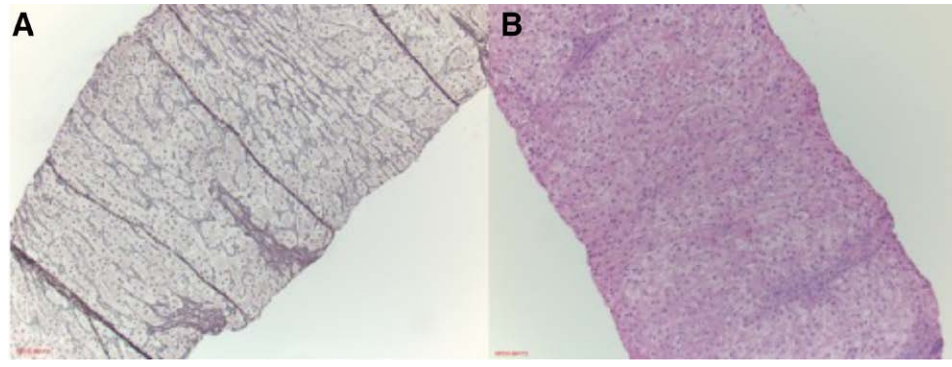


**FIGURE 4.** Posttransplant biopsy for case 4. Posttransplant biopsy for case 4. The donor was a pediatric patient with no pretransplant biopsy performed. A, Reticulin stain showing subtly alternately expanded and compressed hepatic plates, suggestive of NRH (reticulin, ×100). B, Biopsy of posttransplant liver in H&E stain (×100) showing evidence of NRH. H&E, hematoxylin and eosin; NRH, nodular regenerative hyperplasia.

## CASE 4

Patient 4 is a 4-y-old male child with end-stage liver disease because of progressive familial intrahepatic cholestasis and normal renal function whose DBD was a previously healthy 11-y-old girl child. The donor organ was placed on the TransMedics OCS for 4 h and 55 min. The patient was transplanted with the left lateral segment of the donor organ in a piggyback manner with no intraoperative hypotension. POD 1 laboratory tests showed BUN 23 mg/dL, Cr 0.4 mg/dL, AST 743 U/L, ALT 556 U/L, ALP 99 IU/L, and platelets 111/L. He was started on tacrolimus and methylprednisone. On POD 3 he developed an oliguric AKI with Cr to 0.8 mg/dL. He received trials of albumin and diuretics with stability in his renal function; however, he developed progressive ascites. Doppler ultrasound showed normal hepatic vascular flow and venogram was normal. He underwent percutaneous liver biopsy 7 wk post-LT with pathology negative for T cell–mediated rejection but concerning for NRH (Figure 4). At 9 wk post-LT, the patient underwent a transjugular liver biopsy, which demonstrated mild narrowing of his suprahepatic IVC, a portosystemic gradient of 17 mm Hg, and an RA pressure of 9 mm Hg with pathology findings similar to prior. Additional workup for causes of portal hypertension was unrevealing. Because of concern that the patient's mildly narrowed suprahepatic IVC was contributing to his symptoms, he underwent successful IVC angioplasty as well as left hepatic vein angioplasty 12 wk post-LT. His hospitalization was prolonged by difficulty maintaining volume control, and he was discharged home 16 wk post-LT with maintenance diuretics.

## DISCUSSION

NRH is idiopathic in its origin because it is believed to be a hyperproliferative response to vascular flow abnormalities leading to varying parenchymal perfusion.[3,4] Although post-LT portal hypertension resulting from NRH was previously thought to be rare, new data suggest that up to 5.1% of patients post-LT develop NRH leading to CSPH in 25.2% of those patients.[5] Yet studies cite the average time from LT to diagnosis of NRH as 6.6 y[6] with an average time to the onset of symptoms as 8.4 y[5] with no prior cases documenting the diagnosis and development of symptoms as rapidly post-LT as presented here. Although this case series represents a minority of posttransplant patients at our institution with pump parameters (Table 1) comparable with other patient cases, we hypothesize that use of normothermic perfusion pumps combined with patient factors may be linked to the rapid development of posttransplant NRH by contributing to vascular flow abnormalities. Treatment of NRH is typically directed at treating the underlying disorder, with supportive measures for complications from resulting portal hypertension. These patients experienced improvement in portal hypertension symptoms, which is not typical for NRH, suggesting that supportive care, including short-term RRT, may help bridge patients through the most symptomatic period. Data from other transplant centers are needed to determine whether similar clinical cases have occurred elsewhere. Future studies should explore whether perfusion pump use may contribute to NRH development.

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