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Hilar Biliary Amputation Neuroma Following Liver Transplant: A Case Report and Review of the Literature for this Diagnostic and Therapeutic Challenge

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INTRODUCTION

Hilar amputation neuroma (HAN), also known as traumatic neuroma, is a benign lesion that originates from reactive hyperplasia of peripheral nerve fibers in the hilar region previously exposed to surgical transection.[1,2] HANs have been previously associated with surgeries such as cholecystectomy, but have also been reported as a complication in liver transplant (LT) patients. Many post-LT HANs are asymptomatic with a nonprogressive clinical course. However, they can advance to cause a biliary anastomotic stricture, which is often refractory to standard endoscopic interventions and can contribute to allograft loss.[3] The diagnosis of HANs is elusive because there are no characteristic clinical or imaging manifestations, and thus histopathologic examination is required to establish the diagnosis.[3] Here, we report the case of an HAN that led to repeat LT and subsequently summarize all available published data on HANs to promote awareness of the diagnostic and therapeutic challenges surrounding this entity.

CASE

A 49-y-old man with alcohol-associated cirrhosis complicated by hepatocellular carcinoma underwent orthotopic LT with a duct-to-duct biliary anastomosis. Upon discharge, his immunosuppression regimen consisted of tacrolimus, mycophenolic acid, and a prednisone taper over several weeks. Two weeks later, due to rising alkaline phosphatase and bilirubin levels, endoscopic retrograde cholangiopancreatography (ERCP) revealed a moderate biliary anastomotic stricture and a plastic stent was placed (Figure 1). He subsequently had normalization of his liver tests, but required 4 additional ERCPs in the first 9 mo post-LT for follow-up on the stricture. These ERCPs revealed occluded biliary stents with a persistent anastomotic stricture that was

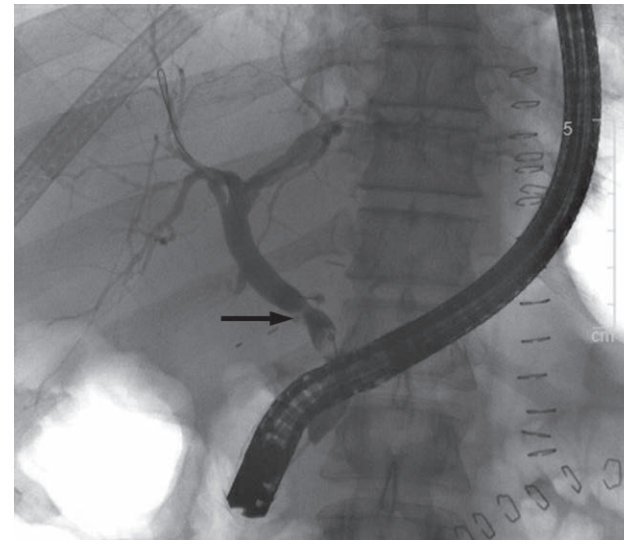

FIGURE 1. Cholangiogram during endoscopic retrograde cholangiopancreatography demonstrating anastomotic stricture (arrowed).

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Signed informed consent was obtained in the patient's preferred language from the patient and can be made available upon request.

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then dilated and restented, and choledocholithiasis upon sweep for which the patient was already taking stone dissolution dosing of ursodeoxycholic acid. Given stability in his liver chemistries and sustained goal tacrolimus levels, the patient's immunosuppression regimen was adjusted to tacrolimus monotherapy at 10 mo post-LT. Follow-up ERCP at this time was performed for stent exchange. Nearly 1 y after LT, the patient developed progressively worsening liver injury in a predominantly cholestatic pattern (bilirubin—28 mg/dL, direct—19.5 mg/dL; alkaline phosphatase—206 U/L; aspartate aminotransferase—206 U/L; alanine aminotransferase—215 U/L, international normalized ratio—2.0). Computed tomography (CT) scan revealed patent hepatic vasculature and no biliary dilatation or masses but did demonstrate nonspecific hilar stranding. Phosphatidylethanol levels and polymerase chain reactions for cytomegalovirus, Epstein-Barr virus, herpes simplex virus 1 and 2, varicella zoster, human herpesvirus 6 and 7, and hepatitis B, C, and E were all undetectable. Liver biopsy demonstrated bile duct epithelial and luminal neutrophils with pigment-laden histiocytes within portal and periportal regions and periportal fibrosis compatible with extrahepatic biliary obstruction. The next day, ERCP was conducted, which demonstrated occluded stents, anastomotic biliary stricture, and sludge for which stenting was performed. Two days later, repeat ERCP was performed for placement of a fully covered metal stent. Unfortunately, this intervention did not lead to any improvement in cholestasis. Two weeks later and now 1-y post-LT, a final ERCP did not reveal a definite biliary stricture or stones, yet markedly delayed drainage of contrast was noted and the biliary anastomosis was noted to appear slightly irregular, therefore several stents were placed. Bile was observed flowing through these stents. Surgical management of stricture was discussed but ultimately not pursued as no clear stricture was noted on the final cholangiogram. At this time, repeat biopsy revealed ductopenia (12 of 20 portal triads) and cholate stasis, a finding resulting from chronic cholestasis, characterized by hydropic periportal hepatocytes with foamy pseudoxanthomatous changes. Overall, these findings suggested ongoing, severe extrahepatic biliary obstruction. The C4d stain, to assess for antibody-mediated rejection, was negative. However, because of mild venulitis and ductopenia seen on this repeat biopsy, immunosuppression was preemptively increased to include prednisone and mycophenolic acid in addition to increased tacrolimus dosage to address possible overlapping acute on chronic rejection, but with no improvement (bilirubin—25 mg/dL, direct—18 mg/dL; alkaline phosphatase—156 U/L; aspartate aminotransferase—58 U/L; alanine aminotransferase—86 U/L, international normalized ratio—2.1). Importantly, tacrolimus levels were at goal leading up to this period and pharmacy fill history suggested medication adherence. The patient was listed for retransplantation under the presumption of chronic rejection causing graft loss. One month later, (13 mo post-LT), he subsequently underwent retransplantation with hepaticojejunostomy creation. Of note, the patient's common bile duct (CBD) was noted as severely dilated and diseased during the operation. There has been no recurrent cholestasis since. Pathologic review of the explant revealed a 1.2-cm white dense hilar mass microscopically characterized by haphazardly arranged nerve fibers showing immune-positivity for S100 neural biomarker by immunohistochemistry consistent with Schwann cells with intervening collagenous scar dispersing into adjacent liver parenchyma diagnostic of neuroma within the biliary hilum of the explanted liver (Figure 2A, B). Adjacent hepatocytes showed marked cholestasis with coalescing pools of bile infarct. Microscopy of hilum and liver parenchyma did not demonstrate obliterative arteriopathy or any significant ductopenia to suggest chronic rejection, therefore the cause of this patient's graft dysfunction and subsequent retransplantation is attributed to biliary obstruction due to the HAN and not chronic rejection. Now, over 2 y since re-LT, the patient is doing well clinically and graft function is robust.

DISCUSSION

Within hours, the Schwann cells at the proximal endings of peripheral nerves that have been transected attempt to restore continuity by building a sheath to bridge the defect. However, if the distance between the endings is too wide, then fibrous granulation tissues arise, which precludes regeneration.[4]

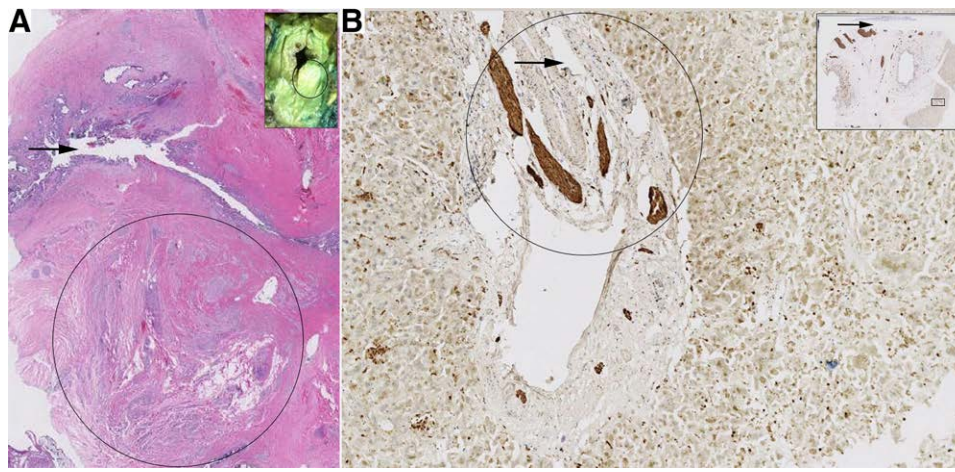

FIGURE 2. A, Gross image of the common bile duct with a neuroma (encircled) shown in the inset. The common bile duct lumen (arrowed) is adjacent to a neuroma (encircled) shown in the main image (H and E stain; 2X magnification). B, An S100 immunostain (dark brown) highlighting a neuroma within the common bile duct (arrowed) shown in the inset. An S100 immunostain (dark brown, 10X magnification) highlighting the neuroma (encircled) infiltrating into a portal tract (arrowed) of adjacent liver shown in the main image that corresponds to the area delineated by a rectangle within the inset.

TABLE 1.

Characteristics of reported cases symptomatic HANs of in the literature

Series y	Patients in series	Recipient age and gender	Indication for previous LT	Time to symptom onset (mo)	Type of biliary anastomosis	Clinical presentation	Diagnostic test(s)	Therapeutic interventions (in sequential order)	Histology results on explant or surgical specimen	Neuroma size (mm)	Outcome
Current case (Thaker, Mikolajczyk, 2021)	1	49 M	Alcohol-associated cirrhosis/hepatocellular carcinoma	0.5	E-E	Abnormal liver enzymes	ERCP, liver biopsy, CT, US	Endoscopic stenting, re-LT with HJ	Cholestasis	15	No recurrence at 1-y post-LT
Colina et al (1994)[3]	1	50 M	Alcohol-associated cirrhosis/hepatocellular carcinoma	6	E-E	Cholangitis	US, transhepatic cholangiography	Percutaneous biliary drainage	Cholestasis	<25	Extrahepatic biliary leak; death from sepsis
Mrzljak et al (2020)[1]	1	54 M	Alcohol-associated cirrhosis/hepatocellular carcinoma	N/A	E-E	Jaundice	CT, MRCP	Re-LT	Cholestasis, HAT, PVT	15	
	2	32 F	Primary biliary cholangitis	N/A	E-E	Jaundice, pruritus	MRCP	Re-LT	Ischemic biliary lesions, cholestasis	17	
	3	54 M	Re-LT, cholangitis	N/A	H-J	Abdominal discomfort	CT, MRCP	Re-LT	HAT, necrosis	30	
	4	58 M	Alcohol-associated cirrhosis/hepatocellular carcinoma	N/A	E-E	Recurrent dilatation	MRCP, CT, ERCP	Endoscopic balloon dilation, re-LT	Cholestasis, ischemic biliary lesions	30	
	5	60 M	Alcohol-associated cirrhosis	N/A	E-E	Jaundice	MRCP	HJ creation, revision of HJ, re-LT	Cholestasis, fibrosis	25	
	6	64 M	Alcohol-associated cirrhosis	N/A	E-E	Jaundice	MRCP	Percutaneous biliary drainage, re-LT	Cholestasis, cirrhosis	30	
	7	60 M	Primary biliary cholangitis	N/A	E-E	Jaundice	MRCP, CT	Re-LT	HAT, fibrosis, cholestasis	20	
Mentha et al (1999)[2]	1	59 M	Hepatitis B cirrhosis/hepatocellular carcinoma	17	E-E	Abnormal liver enzymes	US, MRI	Percutaneous balloon dilation, HAN resection, and HJ creation	Infiltrating traumatic neuroma on resection specimen	10	Discharged after 29 d
	2	46 M	Hepatitis B cirrhosis	4	E-E	Abnormal liver enzymes	US, transhepatic cholangiography	Percutaneous balloon dilation and stenting, HJ creation	Traumatic neuroma on resection specimen	2	
Herrera et al (2009)[6]	1	N/A	N/A	6	E-E	Jaundice	ERCP	Endoscopic dilation, resection with E-E anastomosis revision	Chronic inflammation, fibrosis	N/A	Died traffic accident
	2	N/A	N/A	9	E-E	Jaundice	Re-LT	Re-LT	Hilar traumatic neuroma	N/A	Well
	3	N/A	N/A	17	E-E	Jaundice	ERCP	Resection, HJ creation	Chronic inflammation	N/A	Biliary sepsis
	4	N/A	N/A	2	E-E	Jaundice	ERCP	Endoscopic balloon dilation, resection with E-E anastomosis revision		N/A	Hepatitis C recurrence
	5	N/A	N/A	12	E-E	Jaundice	ERCP	Resection with E-E anastomosis revision	Mild chronic inflammation, epithelial loss	N/A	Hepatitis C cirrhosis recurrence

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TABLE 1 (Continued)

Characteristics of reported cases symptomatic HANs of in the literature

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	6	N/A	N/A	9	E-E	Jaundice	ERCP	Endoscopic balloon dilation, resection with E-E anastomosis revision	Chronic inflammation	N/A	Hepatitis C cirrhosis recurrence, mesenteric thrombosis
	7	N/A	N/A	1	E-E	Jaundice	US, ERCP	Resection with E-E anastomosis revision	Ischemic necrosis	N/A	Well
	8	N/A	N/A	12	E-E	Jaundice	Incidental	Left hepatectomy, re-LT	Hilar traumatic neuroma	N/A	Well
	9	N/A	N/A	2	E-E	Jaundice	ERCP	Resection with E-E anastomosis revision	Fibrosis, chronic inflammation, and granulomatous reaction to foreign body	N/A	Lung adenocarcinoma, Normal biliary US
	10	N/A	N/A	18	E-E	Jaundice	CT, MRCP	Balloon dilation, HJ creation	Chronic inflammation	N/A	Chronic rejection requiring re-LT, mesenteric thrombosis
	11	N/A	N/A	4	E-E	Abnormal liver enzymes	MRCP	HJ creation	Subtotal necrosis of CBD; initial TN	N/A	Cholangitis, MRCP with mild biliary stenosis
	12	N/A	N/A	2	E-E	Jaundice	ERCP	Endoscopic balloon dilation and stenting, HJ creation	Chronic and acute inflammation secondary neuritis and perineuritis	N/A	Well; normal biliary US
	13	N/A	N/A	1	E-E	Abnormal liver enzymes	T-tube cholangiogram, ERCP	Endoscopic balloon dilation, resection with E-E anastomosis revision	Traumatic neuroma, chronic inflammation, necrotizing granuloma	N/A	Well
	14	N/A	N/A	1	E-E	Jaundice	US, MRCP	H-J, re-LT	Granulomatous reaction to foreign body (suture), traumatic neuroma	N/A	Postoperative death
	15	N/A	N/A	4	E-E	Abnormal liver enzymes	US, MRCP	Resection with E-E anastomosis revision	Chronic inflammation and fibrosis	N/A	Well
Navez et al (2016)[8]	1	N/A	Alcohol-associated cirrhosis	239	E-E	Bile leak, biliary stricture	MRCP	Resection with E-E anastomosis revision	N/A	N/A	Acute pancreatitis, death 21 d post-neuroma treatment
	2	N/A	Cryptogenic cirrhosis	162	E-E	Cholangitis, biliary stricture	US, MRCP	Resection and HJ creation	N/A	N/A	Well at 54 mo post-neuroma treatment
	3	N/A	Alcohol-associated cirrhosis	69	E-E	Cholangitis, biliary stricture	US, MRCP	Endoscopic drainage, resection, and HJ creation	N/A	N/A	Well at 49 mo post-neuroma treatment
	4	N/A	Recurrent hepatitis C cirrhosis	31	E-E	Jaundice, biliary stricture	US, CT, MRCP	Resection and HJ creation	N/A	N/A	Well at 32 mo post-neuroma treatment

TABLE 1 (Continued)

Characteristics of reported cases symptomatic HANs of in the literature

Series y	Patients in series	Recipient age and gender	Indication for previous LT	Time to symptom onset (mo)	Type of biliary anastomosis	Clinical presentation	Diagnostic test(s)	Therapeutic interventions (in sequential order)	Histology results on explant or surgical specimen	Neuroma size (mm)	Outcome
	5	N/A	Alcohol-associated cirrhosis	4	E-E	Abnormal liver enzymes, biliary stricture	US, CT, MRCP	Percutaneous drainage, resection, and HJ creation	N/A	N/A	Well at 10 mo post-neuroma treatment
Nachtwey et al (1997)[9]	1	43 M	Hepatitis C cirrhosis	6	E-E	Abnormal liver enzymes	US, ERCP, liver biopsy	Failed dilation, re-LT, and HJ creation	Neuroma compressing hepatic artery, HAT, hepatic infarctions	50	Well at 12 mo follow up
Terzi et al (2017)[10]	1	17 F	Autoimmune hepatitis with cirrhosis	3	E-E	Bile leak	ERCP, liver biopsy	Endoscopic stenting and dilation, HJ creation	Cholestasis, ischemia	4	Ductopenic chronic rejection
Gonzalez-Pinto et al (1997)[11]	1	38 M	Alcohol-associated cirrhosis	18	E-E	Abnormal liver enzymes	US, transhepatic cholangiography	Resection and HJ creation, re-LT later	Necrosis of wall of the stenotic perianastomotic bile ducts with inflammatory tissue, graft with fibrous neuroma surrounding and compressing hepatic artery and fibrous stenoses of intrahepatic bile ducts	30	Well at 2 y post-re-LT

CBD, common bile duct; CT, computed tomography; E-E, end-to-end; ERCP, endoscopic retrograde cholangiopancreatography; HAN, hilar implantation neuroma; HAT, hepatic artery thrombosis; HJ, hepaticojejunostomy; LT, liver transplantation; MRCP, magnetic resonance cholangiopancreatography; N/A, not available; PVT, portal vein thrombosis; US, ultrasonography.

The proliferating Schwann cells and fibroblasts form benign nodules called traumatic neuromas. The liver has rich sympathetic and parasympathetic innervation, which regulates many functions including choleresis.[5] These nerve fibers are organized into an anterior trunk accompanying the hepatic artery and posterior trunk accompanying the portal vein and CBD in the hilum. HANs (ie, traumatic neuromas of the hilum) can develop from either donor or recipient neural tissue after the transection of these nerve bundles during LT. Due to external compression of the CBD, HANs can cause anastomotic strictures, like our patient's initial presentation. In addition, as our case also demonstrated, HANs can be characterized by an infiltrative growth pattern. The end result is likely compromised choleretic, which would explain the marked delay in the flow of contrast without definite obstruction on our patient's final cholangiogram and why the HAN was not apparent during the retransplantation.

In addition to our case, there have been 58 additional published cases of post-LT HANs in case reports and case series from 1994 to 2020. The true incidence of HAN post-LT is likely underestimated as its diagnosis requires histopathologic analysis.[3,6] Colina et al first described HAN in OLT recipients with a reported incidence of 27.9% (n = 26) after histopathological examination of 93 explants and autopsy specimens. The size of the neuroma ranged from 4 to 50 mm (mean 22.38 ± 11.06 mm). All cases were immunoreactive with S100 antibody by immunohistochemistry confirming neural tissue differentiation. Notably, there is also a documented case of HAN occurring in a donor (living donor LT) after an 8-y interval.[7]

All of the patients in the aforementioned series were asymptomatic except for 1 case (1%).[3] Two other series report an incidence of symptomatic HAN ranging from 0.5% to 6.1% (7 of 101 undergoing repeat LT).[1,8] Of these symptomatic cases (Table 1), the majority presented with jaundice and/or cholangitis (22 of 34), and the time from LT to symptoms was variable (0.5–239 mo, 24.4 mo mean, 6 mo median). Nearly all of these cases (97.1%, 33 of 34) of symptomatic HAN post-LT are associated with duct-to-duct biliary anastomosis at initial LT. A single case was noted to have abnormal imaging showing a compressive mass, whereas the remaining 33 cases did not report notable imaging findings.[8] In our case, the nonspecific hilar stranding noted on a single CT scan may have been signs of HAN formation. Of 34 cases, 21 underwent either endoscopic of percutaneous biliary procedure (61.8%), and 33 of 34 cases required definitive surgical treatments, which included HAN resection with revision of end-to-end biliary anastomosis (n = 9, 26.4% of those who underwent surgery), HAN resection and hepaticojejunostomy creation (n = 12, 35.3%), and/or retransplantation (n = 13, 38.2%; 3 of which had a different prior surgical intervention). This lack of response to nonsurgical interventions is due to poor compressibility of these highly fibrotic tumors, but can also be due to local infiltration of HAN nerve fibers into adjacent liver parenchyma and the hepatic artery as reported in our case and 1 other, respectively.[1,9] HAN recurrence has not been reported thus far in the limited series published.

In summary, increased awareness and recognition of this LT complication are needed. Suspicion for an HAN should heighten when one encounters a refractory biliary stricture and/or cholestasis post-LT that are not responsive to nonsurgical interventions, such as biliary stenting, dilatation, and

drainage. Given the difficulty in diagnosing this entity and that treatment is surgical, early discussions about surgical management (eg, hepaticojejunostomy creation) may offer a chance at graft salvage before retransplantation. Further studies on the risk factors, diagnosis, and optimal management for HANs after LT are desperately needed.

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