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

Sarang Thaker, MD, MS,1 Najib Nassani, MD, MSc,2 Bartlomiej Lukasz Radzik, MD,3 Christine Chan, MD,1 Wadih Chacra, MD,1 Sean Koppe, MD,1 Grace Guzman, MD,3 and Adam E. Mikolajczyk, MD1

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.1 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).
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. Phosphatidylethanolamine 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 structure 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 hepatojejunostomy 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 obliterator 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 ends 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 tests(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) | 1 | 50 M | Alcohol-associated cirrhosis/hepatocellular carcinoma | 6 | E-E | Cholangitis | US, transhepatic Percutaneous biliary cholangiography drainage | Cholestasis | <25 | Extrabiliary biliary leak; death from sepsis |
| Mrzljak et al (2020) | 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, US, MRI | Percutaneous balloon dilation, HAN resection, and HJ creation | HAT, fibrosis, cholestasis | 20 |
| Mentha et al (1999) | 1 | 59 M | Hepatitis B cirrhosis/hepatocellular carcinoma | 17 | E-E | Abnormal liver enzymes | MRCP, CT | Re-LT | 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) | 1 | N/A | N/A | 6 | E-E | Jaundice | ERCP | Endoscopic dilation, resection with E-E anastomosis revision | Chronic inflammation, fibrosis | NA | Died traffic accident |
| | 2 | N/A | N/A | 9 | E-E | Jaundice | Re-LT | Hilar traumatic neuroma post-LT | NA | Well |
| | 3 | N/A | N/A | 17 | E-E | Jaundice | ERCP | Resection, HJ creation | NA | Biliary sepsis |
| | 4 | N/A | N/A | 2 | E-E | Jaundice | ERCP | Endoscopic balloon dilation, resection with E-E anastomosis revision | Hilar fibrosis | NA | Hepatitis C recurrence |
| | 5 | N/A | N/A | 12 | E-E | Jaundice | ERCP | Resection with E-E anastomosis revision | Mild chronic inflammation, epithelial loss | NA | Hepatitis C cirrhosis recurrence |

Continued next page
| Series y | Patients in series | Recipient age and gender | Clinical presentation | Time to symptom onset (mo) | Indication for previous LT | Type of biliary anastomosis | Therapeutic interventions (in sequential order) | Histology results on explant or surgical specimen | Outcome |
|----------|-------------------|-------------------------|----------------------|---------------------------|---------------------------|-----------------------------|----------------------------------|-----------------------------------|---------|
| 6        | N/A               | N/A                     | Jaundice             | 9                         | E-E                       | Endoscopic balloon dilation, Chronic inflammation | N/A                               | N/A                               | Well; normal biliary stenoses |
| 7        | N/A               | N/A                     | Jaundice             | 1                         | E-E                       | Resection with E-E anastomosis revision | N/A                               | N/A                               | Well |
| 8        | N/A               | N/A                     | Jaundice             | 12                        | E-E                       | Resection with E-E anastomosis revision | N/A                               | N/A                               | Chronic rejection |
| 9        | N/A               | N/A                     | Jaundice             | 2                         | E-E                       | Endoscopic balloon dilation, Chronic inflammation; Ischemic necrosis | N/A                               | N/A                               | Chronic rejection, mesenteric thrombosis |
| 10       | N/A               | N/A                     | Jaundice             | 18                        | E-E                       | Subtotal necrosis of CBD; Initial TN | N/A                               | N/A                               | Well |
| 11       | N/A               | N/A                     | Jaundice             | 4                         | E-E                       | Abnormal liver enzymes | ERCP                               | N/A                               | Well |
| 12       | N/A               | N/A                     | Jaundice             | 2                         | E-E                       | Abnormal liver enzymes | MRCP                               | N/A                               | Well |
| 13       | N/A               | N/A                     | Jaundice             | 1                         | E-E                       | Abnormal liver enzymes | ERCP; T-tube cholangiogram | N/A                               | Well |
| 14       | N/A               | N/A                     | Jaundice             | 1                         | E-E                       | Abnormal liver enzymes | MRCP; US, MRCP                  | N/A                               | Well |
| 15       | N/A               | N/A                     | Jaundice             | 4                         | E-E                       | Abnormal liver enzymes | ERCP; MRCP; US, MRCP; MRCP; MRCP; US, MRCP | N/A                               | Well |

**TABLE 1 (Continued)**

Characteristics of reported cases symptomatic HANs of the literature

| Series y | Patients in series | Recipient age and gender | Clinical presentation | Time to symptom onset (mo) | Indication for previous LT | Type of biliary anastomosis | Therapeutic interventions (in sequential order) | Histology results on explant or surgical specimen | Outcome |
|----------|-------------------|-------------------------|----------------------|---------------------------|---------------------------|-----------------------------|----------------------------------|-----------------------------------|---------|
| 14       | N/A               | N/A                     | Jaundice             | 4                         | E-E                       | Resection with E-E anastomosis revision | N/A                               | N/A                               | Well |
| 15       | N/A               | N/A                     | Jaundice             | 4                         | E-E                       | Resection with E-E anastomosis revision | N/A                               | N/A                               | Well |

**Navez et al (2016)**

- **Series y:** N/A
- **Patients in series:** N/A
- **Recipient age and gender:** N/A
- **Clinical presentation:** Jaundice
- **Time to symptom onset (mo):** 1
- **Indication for previous LT:** Alcohol-associated cirrhosis
- **Type of biliary anastomosis:** US, MRCP
- **Therapeutic interventions (in sequential order):** Resection and HJ creation
- **Histology results on explant or surgical specimen:** N/A
- **Outcome:** Well at 49 mo post-neuroma treatment

**2** | N/A | N/A | Jaundice | 1 | E-E | Jaundice | MRCP; US, MRCP | N/A | Well |

**3** | N/A | N/A | Jaundice | 69 | E-E | Jaundice | MRCP; US, MRCP | N/A | Well |

**4** | N/A | N/A | Jaundice | 31 | E-E | Jaundice | MRCP; US, MRCP | N/A | Well |

**5** | N/A | N/A | Jaundice | 46 | E-E | Jaundice | Resection and HJ creation | N/A | Well |

**6** | N/A | N/A | Jaundice | 50 | E-E | Jaundice | Resection and HJ creation | N/A | Well |

**7** | N/A | N/A | Jaundice | 60 | E-E | Jaundice | Resection and HJ creation | N/A | Well |

**8** | N/A | N/A | Jaundice | 70 | E-E | Jaundice | Resection and HJ creation | N/A | Well |

**9** | N/A | N/A | Jaundice | 80 | E-E | Jaundice | Resection and HJ creation | N/A | Well |

**10** | N/A | N/A | Jaundice | 90 | E-E | Jaundice | Resection and HJ creation | N/A | Well |

**11** | N/A | N/A | Jaundice | 100 | E-E | Jaundice | Resection and HJ creation | N/A | Well |

**12** | N/A | N/A | Jaundice | 110 | E-E | Jaundice | Resection and HJ creation | N/A | Well |

**13** | N/A | N/A | Jaundice | 120 | E-E | Jaundice | Resection and HJ creation | N/A | Well |

**14** | N/A | N/A | Jaundice | 130 | E-E | Jaundice | Resection and HJ creation | N/A | Well |

**15** | N/A | N/A | Jaundice | 140 | E-E | Jaundice | Resection and HJ creation | N/A | Well |
Characteristics of reported cases symptomatic HANs of in the literature

| Recipient | Time to symptom onset (mo) | Type of biliary anastomosis | Outcome | Neurona size (mm) |
|-----------|---------------------------|-----------------------------|---------|-----------------|
| Patients in series | | | | |
| Nachon et al (1997) | 5 | N/A | Well at 10 mo post-neo | N/A |
| Nachtwey et al (1997) | 1 | 43 M | Alcohol-associated cirrhosis | 4 | E-E | Abnormal liver enzymes, biliary stricture | US, CT, MRCP | Percutaneous drainage, re-LT, and HJ creation |
| Terzi et al (2017) | 1 | 17 F | Autoimmune hepatitis with cirrhosis | 3 | E-E | Abnormal liver enzymes, bile leak | ERCP, liver biopsy | Endoscopic stenting and dilation, HJ creation, re-LT later |
| Gonzalez-Pinto et al (1997) | 18 | 38 M | Alcohol-associated cirrhosis | 18 | E-E | Abnormal liver enzymes, bile leak | ERCP, liver biopsy | Endoscopic stenting and dilation, HJ creation, re-LT later |

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 cholestasis.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 histopathological 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 cholestasis post-LT that are not responsive to nonsurgical interventions. 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 surgical interventions, such as biliary stenting, dilatation, and/or cholestasis post-LT. Of 93 cases, 21 underwent either endoscopic or 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 surgical interventions, such as biliary stenting, dilatation, and/or cholestasis post-LT. Of 93 cases, 21 underwent either endoscopic or 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 = 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.
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.

REFERENCES

1. Mrzljak A, Skrtic A, Gasparov S, et al. Traumatic neuroma and liver retransplant. Exp Clin Transplant. Apr 7 2020.
2. Mentha G, Rubbia-Brandt L, Orci L, et al. Traumatic neuroma with biliary duct obstruction after orthotopic liver transplantation. Transplantation. 1999;67:177–179.
3. Colina F, García-Prats MD, Moreno E, et al. Amputation neuroma of the hepatic hilum after orthotopic liver transplantation. Histopathology. 1994;25:151–157.
4. Oliveira KMC, Pindur L, Han Z, et al. Time course of traumatic neuroma development. PLoS One. 2018;13:e0200548–e0200548.
5. Terada T, Nakanuma Y. Innervation of intrahepatic bile ducts and peribiliary glands in normal human livers, extrahepatic biliary obstruction and hepatolithiasis. An immunohistochemical study. J Hepatol. 1989;9:141–148.
6. Herrero L, Martino E, Rodríguez-Sanjuán JC, et al. Traumatic neuroma of extrahepatic bile ducts after orthotopic liver transplantation. Transplant Proc. 2009;41:1054–1056.
7. Kim NR, Cho HY, Chung DH, et al. Post-transplant amputation traumatic neuroma of the hilum and extrahepatic duct in a liver donor. J Pathol Transl Med. 2018;52:191–194.
8. Navez J, Golse N, Bancel B, et al. Traumatic biliary neuroma after orthotopic liver transplantation: a possible cause of “unexplained” anastomotic biliary stricture. Clin Transplant. 2016;30:1366–1369.
9. Nachtwey BA, Rogiers X, Waldstroem J, et al. Hilar traumatic neuroma after liver transplantation. Transpl Int. 1997;10:157–160.
10. Terzi A, Kirnap M, Sercan C, et al. Traumatic neuroma causing biliary stenosis after orthotopic liver transplant, treated with hepaticojejunostomy: a case report. Exp Clin Transplant. 2017;15(Suppl 1):175–177.
11. Gonzalez-Pinto IM, Castellano VM, Moreno-González E, et al. Hepatic artery thrombosis as a complication of amputation neuroma of the liver graft hilum. Transpl Int. 1997;10:405–406.