Neuroendocrine Tumor of the Common Bile Duct Associated With von Hippel-Lindau Disease

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ABSTRACT
We report a case of a common bile duct neuroendocrine tumor discovered in a patient with von Hippel-Lindau disease to emphasize the importance of recognizing this unusual diagnosis. This case illustrates the importance of endoscopic evaluation and the potential diagnostic pitfalls which may impact its appropriate management: the anatomic proximity of more common von Hippel-Lindau disease–related tumors, pathologic evaluation, and staging. Therefore, awareness of this rare diagnosis is important for appropriate treatment.

INTRODUCTION
von Hippel-Lindau (VHL) disease is a hereditary cancer syndrome characterized by a spectrum of tumors of the pancreas, kidney, adrenal gland, eye, ear, central nervous system, and genital tract.1,2 Mutation of the VHL gene dysregulates the ubiquitination and degradation of hypoxia-inducible factor.1 Extrahepatic biliary neuroendocrine tumors (NETs) account for 0.2%–2% of all gastrointestinal NETs.3 The presence of extrahepatic biliary NETs as a manifestation of VHL is exceedingly rare with only 3 previous cases described in the literature.4–6

CASE REPORT
A 75-year-old woman with VHL disease presented before her scheduled interval follow-up of her nonfunctional pancreatic NETs (pNETs) with intermittent epigastric pain and nausea. She had been undergoing surveillance imaging over the previous 3 years for multiple pancreatic body and tail pNETs, the largest of which was 1.2 × 1.6 cm. Her physical examination was unremarkable while laboratory studies revealed an elevated alkaline phosphatase 211 U/L, aspartate aminotransferase 84 U/L, alanine aminotransferase 214 U/L, direct bilirubin 0.6 mg/dL, total bilirubin 1.0 mg/dL, and chromogranin A 184 ng/mL. Cross-sectional imaging showed a 1.6-cm peripherally enhancing lesion adjacent to or within the common bile duct (CBD) (Figure 1). To better characterize whether this mass was originating from the bile duct or pancreas, an endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP) with cholangioscopy were performed. EUS confirmed a 1.5 × 1.1-cm hypoechoic mass arising from the submucosa of the mid-CBD with no associated lymphadenopathy (Figure 2). ERCP demonstrated the mass as a round filling defect causing diffuse upstream biliary dilation up to 14 mm (Figure 3). Cholangioscopy was performed to directly visualize the tumor and allow for biopsies. The mass was seen as a smooth, round, hypervascular lesion bulging into the biliary lumen causing partial obstruction (Figure 4). Biopsies were taken through the cholangioscope; however, results were nondiagnostic. Based on the submucosal appearance of the lesion on EUS and the patient’s known diagnosis of VHL, a NET was suspected rather than a distal CBD cholangiocarcinoma.
Given that the tumor was causing biliary obstruction with elevated liver enzymes, operative intervention was indicated. A pancreaticoduodenectomy was considered. However, palpation of the bile duct revealed a solid, firm mass just posterior to the superior border of the pancreatic head. Therefore, an extrahepatic bile duct resection and portal lymphadenectomy was performed with hepaticojejunostomy reconstruction. Gross examination revealed a tan-white to gray, firm lesion within the duct wall. Intraoperative pathologic consultation was not performed. Pathology was significant for a grade 2 well-differentiated NET demonstrating 2 mitotic figures per 10 high-power fields with a Ki-67 of 8%. The tumor cells were positive for synaptophysin, CD56, cytokeratin (AE1:3), and weakly positive for chromogranin (Figure 5). There were no positive lymph nodes identified in the surgical specimen.

DISCUSSION

Extrahepatic biliary NET as a manifestation of VHL disease is an exceedingly rare entity with only 3 cases reported in the literature, 1 involving the gallbladder and 2 involving the CBD (Table 1).4–6 In the absence of VHL, these tumors remain exceptionally rare.3,7–9 The absence of enterochromaffin cells in the biliary tree may explain the low incidence of biliary NETs.6,8,9 Nonetheless, some authors have postulated that intestinal metaplasia of the biliary tract in the setting of chronic inflammation giving rise to enterochromaffin cells as a possible mechanism for NETs of this location.10 The incidence of extrahepatic biliary NETs peaks in the fifth decade of life with a less aggressive natural history in contrast to cholangiocarcinoma, the most common tumor of the extrahepatic biliary tract.3,8 Because of the rarity of this disease in the context of VHL, it is not known whether extrahepatic biliary NETs behave differently in patients with VHL.
The role of EUS and ERCP with cholangioscopy was key to reveal a biliary NET rather than a pNET. Surgery for pNETs in VHL disease is recommended for tumors $\geq 3$ cm in size, those with shorter doubling times, or symptomatic cases. Our patient presented with symptoms of biliary obstruction. If the tumor was compressing the bile duct from the pancreas, a Whipple procedure would be indicated. However, endoscopic workup identified a primary CBD NET allowing for an extrahepatic bile duct resection.

Preoperative diagnosis of biliary NETs is challenging since these tumors are slow growing and largely nonfunctional. Most patients present with symptoms related to mass effect or partial obstruction of the biliary tree. Imaging findings are nonspecific but include biliary dilation or filling defects. Cholangioscopy directly visualized the in situ biliary origin of the tumor. This is the first report of cholangioscopy in VHL. Alternative endoscopic tests carry a poor sensitivity, including brush cytology given that NETs arise from the submucosa. Moreover, fine needle aspiration of small tumors can be challenging and can lead to results that are nondiagnostic or even misinterpreted as cholangiocarcinoma.

The treatment of choice for extrahepatic biliary NET in those without VHL disease is surgical excision. Following the same recommendations in those with VHL, all 4 patients underwent surgical excision of their tumors without reported complications. We argue that the threshold to operate on these tumors should be lower than that applied to pNET. Given the constraints and limited space of the extrahepatic biliary anatomy, smaller lesions can more readily lead to significant biliary symptoms. Previous studies did not report long-term outcomes, and it is difficult to make conclusions about recurrence, morbidity, and mortality related to surgical excision.

The second key aspect of this case is the limitations of staging biliary NETs. Staging NET, as in this case, uses the staging system for distal bile duct tumors (cholangiocarcinoma). Therefore, our patient is T3N0M0 and Stage IIB. Using this staging system suggests that the patient’s prognosis is grim with a 34% survival at 3 years after surgical resection. Therefore, appreciating this limitation is necessary for framing expectations of both the treating physician and the patient.

To conclude, endoscopic evaluation plays a major role in the correct diagnosis and management of this rare presentation of biliary VHL. Our patient has had no adverse events at 7 months and is undergoing active surveillance with no evidence of early recurrence. Continued reporting of these cases with a focus on long-term follow-up is needed to learn more about this rare disease.

DISCLOSURES

Author contributions: G. Romero-Velez wrote the manuscript. X. Pereira wrote and edited the manuscript. J. Yang edited the manuscript and provided the endoscopic images. NC Panarelli edited the manuscript and prepared the pathological specimens. JC McAuliffe edited the manuscript, approved final version, and is the article guarantor.
Table 1. Characteristics of the reported patients with common bile duct neuroendocrine tumors associated with von Hippel-Lindau disease

| Author, year | Age | Sex | VHL-associated tumors | Presenting symptom | Imaging findings | Location of tumor | Surgery | Pathology |
|--------------|-----|-----|-----------------------|-------------------|-----------------|------------------|---------|-----------|
| Fellows et al, 1990 | 30 | M | Retinal angioma, Renal cell carcinoma | Obstructive jaundice | US: CBD dilation Cholangiogram: filling defect | Junction of the cystic duct and CBD | Bile duct resection with hepaticojejunostomy reconstruction | 1.5-cm carcinoid tumor |
| Sinkre et al, 2001 | 38 | M | Cerebellar hemangioblastoma, Bilateral renal cell carcinoma | Right upper quadrant pain | US: gallbladder mass CT: gallbladder mass | Gallbladder | Lap cholecystectomy | 1.4 × 1.3 × 1-cm, clear-cell carcinoid tumor |
| Nafidi et al, 2008 | 31 | F | Pheochromocytoma, Bilateral renal cell carcinoma | Biliary colic | US: normal ERCP: filling defect of the CBD EUS: intraluminal mass, FNA: negative | CBD | Bile duct resection, portal lymphadenectomy with hepaticojejunostomy reconstruction | 1.2 × 1-cm, well-differentiated carcinoid tumor |
| Romero-Velez et al. | 75 | F | Spinal hemangioblastoma, Retinal hemangioma, Bilateral pheochromocytoma, Pancreatic NET | Epigastric pain | CT: CBD dilation, pancreatic, and CBD NET EUS: intraluminal, submucosal, bile duct mass ERCP + cholangioscopy: mass ERCP with cholangioscopy: CBD mass and biopsies | CBD | Bile duct resection, portal lymphadenectomy with hepaticojejunostomy reconstruction | 1.1 × 1 × 0.8-cm, well-differentiated neuroendocrine tumor (Grade 2), 0/3 lymph nodes |

CBD, common bile duct; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; FHX, family history; FNA, fine needle aspiration; NET, neuroendocrine tumor; US, ultrasound; VHL, von Hippel-Lindau.

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REFERENCES
1. Cassol C, Mete O. Endocrine manifestations of von Hippel-Lindau disease. Arch Pathol Lab Med. 2015;139(2):263–8.
2. van der Horst-Schrivers ANA, Sluiter WJ, Kruizinga RC, et al. The incidence of consecutive manifestations in Von Hippel-Lindau disease. Fam Cancer. 2019;18(3):369–76.
3. Chamberlain RS, Blumgart LH. Carcinoid tumors of the extrabiliary bile duct. Cancer. 1999;86(10):1959–65.
4. Fellows IW, Leach IH, Smith PG, Toghill PJ, Doran J. Carcinoid tumour of the common bile duct: A novel complication of von Hippel-Lindau syndrome. Gut. 1990;31(6):728–9.
5. Sinkre PA, Murakata L, Rabin L, Hoang MP, Albores-Saavedra J. Clear cell carcinoid tumor of the gallbladder: Another distinctive manifestation of von hippel-lindau disease. Am J Surg Pathol. 2001;25(10):1334–9.
6. di ON, Nguyen BN, Roy A. Carcinoid tumor of the common bile duct: A rare complication of von Hippel-Lindau syndrome. WJG. 2008;14(8):1299.
7. Çağlıkulekci M, Dirlik M, Aydin O, et al. Carcinoid tumour of the common bile duct: Report of a case and a review of the literature. Acta Chirurgica Belgica. 2006;106(1):112–5.
8. Kim DH, Song MH, Kim DH. Malignant carcinoid tumor of the common bile duct: Report of a case. Surg Today. 2006;36(5):485–9.
9. Abe T, Nirei A, Suzuki N, et al. Neuroendocrine tumor of the extrabiliary bile duct: A case report. Int J Surg Case Rep. 2017;40:4–9.
10. Barrón-Rodríguez LP, Manivel JC, Méndez-Sánchez N, Jessurun J. Carcinoid tumor of the common bile duct: Evidence for its origin in metaplastic endocrine cells. Am J Gastroenterol. 1991;86(8):1073–6.
11. Howe JR, Merchant NB, Conrad C, et al. The North American Neuroendocrine Tumor Society Consensus Paper on the surgical management of pancreatic neuroendocrine tumors. Pancreas. 2020;49(1):1–33.
12. Boujaoude J, Samaha E, Honein K, et al. A benign cause of obstructive jaundice with von hippel-lindau disease. A case report and review of the literature. JOP. 2016;17:790–4.
13. Strijker M, Belkouz A, van der Geest LG, et al. Treatment and survival of resected and unresected distal cholangiocarcinoma: A nationwide study. Acta Oncol. 2019;58(7):1048–55.

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