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CASE REPORT | BILIARY

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.

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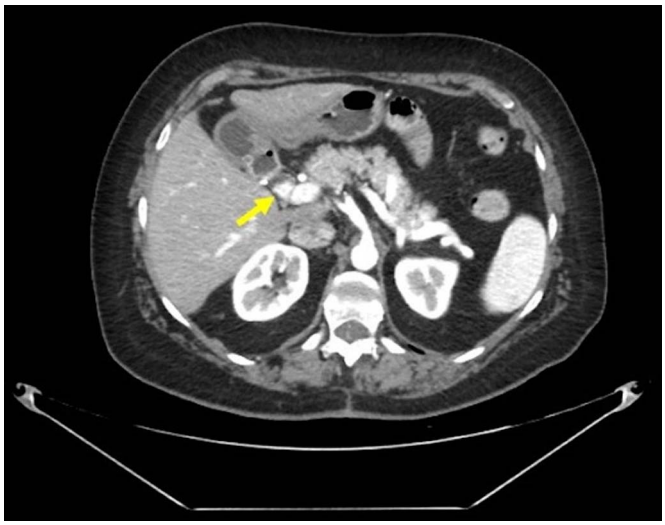

Figure 1. Representative cut of the computed axial tomography of the abdomen. Arrow points to hyperenhancing tumor. Other images (not shown) suggest either biliary, duodenal, or pancreatic origin of tumor.

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.

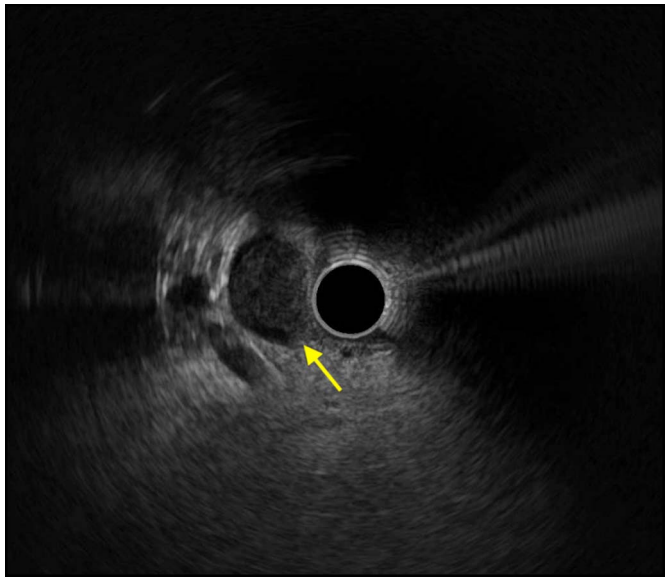

Figure 2. EUS. Arrow showing 1.5-cm hypoechoic CBD tumor. CBD, common bile duct; EUS, endoscopic ultrasound.

There are 2 key aspects of this case requiring attention for optimal management, correct determination of the organ of origin, and the limitations of staging biliary NETs.

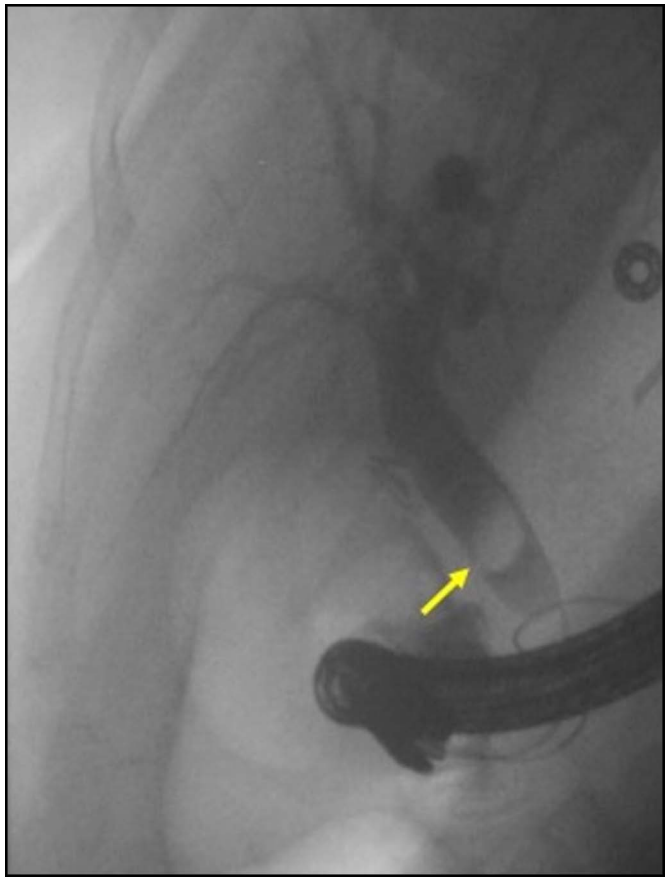

Figure 3. Cholangiogram during ERCP. Arrow points to the CBD tumor. CBD, common bile duct; ERCP, endoscopic retrograde cholangiopancreatography.

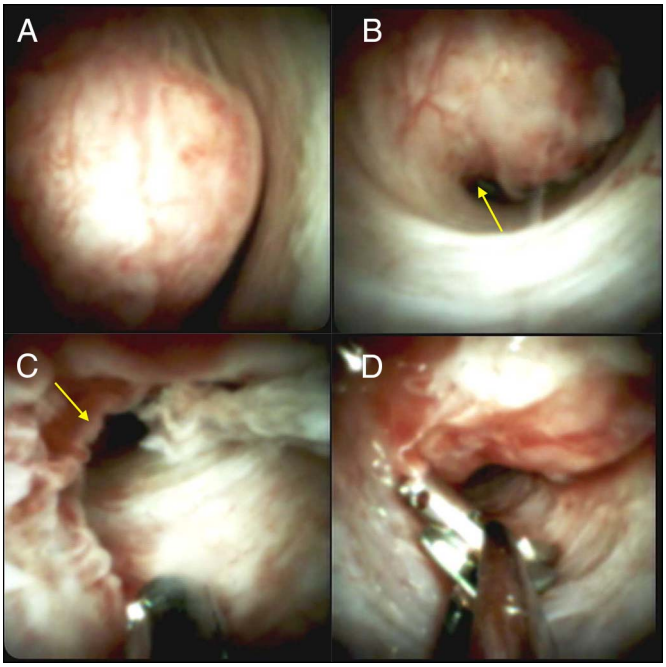

Figure 4. ERCP cholangioscopy (A) visualization of the CBD tumor, (B and C) yellow arrow points to the base of the tumor, and (D) directed biopsies. CBD, common bile duct; ERCP, endoscopic retrograde cholangiopancreatography.

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 ≥3 cm in size, those with shorter doubling times, or symptomatic cases.[11] 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.[11,12] However, endoscopic workup identified a primary CBD NET allowing for an extrahepatic bile duct resection.

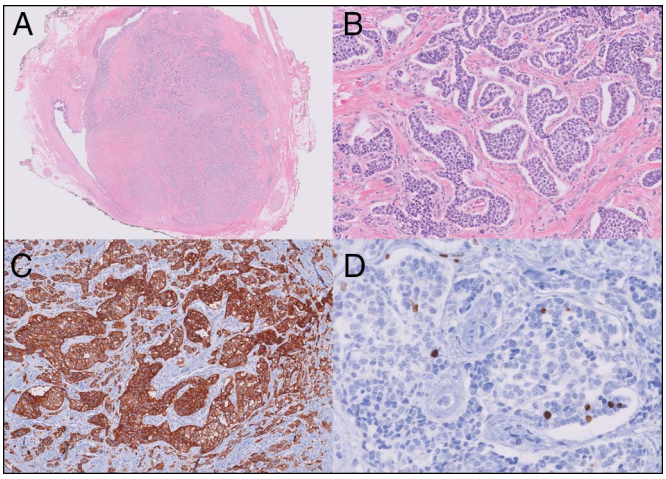

Figure 5. (A) Cross-sections of the bile duct show a circumscribed tumor that distends and partially occludes the bile duct. (B) The tumor comprises nests and trabeculae of round cells with uniform cytology displaying the characteristic "salt and pepper" dispersed chromatin and low mitotic rate of well-differentiated NETs. (C) Strong, diffuse synaptophysin immunolabeling confirms neuroendocrine differentiation. (D) A ki67 immunostaining shows a proliferation rate within the intermediate-grade range. NET, neuroendocrine tumor.

Preoperative diagnosis of biliary NETs is challenging since these tumors are slow growing and largely nonfunctional.[8,9] 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.[3,6]

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.[11] 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.[13] 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.[3,8,9]

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,[4] 1990	30	M	Retinal angioma Renal cell carcinoma FHx of VHL: yes	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,[5] 2001	38	M	Cerebellar hemangioblastoma Bilateral renal cell carcinoma FHx of VHL: unknown	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,[6] 2008	31	F	Pheochromocytoma FHx of VHL: yes	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 FHx of VHL: yes	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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Informed consent was obtained for this case report.

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