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Primary Well-Differentiated Neuroendocrine Tumor of the Perihilar Bile Duct Mimicking Cholangiocarcinoma

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Abstract

Primary neuroendocrine tumors (NETs) of the biliary tract are exceptionally rare and may closely mimic cholangiocarcinoma (CCA). A 73-year-old woman with previous cholecystectomy presented with abdominal discomfort and biliary dilatation. Magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography (MRCP), endoscopic ultrasonography (EUS), endoscopic retrograde cholangiopancreatography (ERCP), and computed tomography (CT) all demonstrated a hilar lesion causing predominantly right-sided biliary obstruction and were considered highly suspicious for perihilar CCA (pCCA); serum carbohydrate antigen 19-9 was 230 U/mL. Endoscopic retrograde cholangiopancreatography-directed forceps biopsy and brush cytology were negative for malignancy. The patient underwent right hepatectomy with en bloc extrahepatic bile duct resection, regional lymphadenectomy, and Roux-en-Y hepaticojejunostomy. Histopathology unexpectedly demonstrated a 4.3 cm well-differentiated grade 2 NET arising in the right and common hepatic duct walls, with a Ki-67 index of 5%, negative margins, and no nodal metastases (0/4). The tumor showed an intramural growth pattern with preserved overlying biliary epithelium, providing a plausible explanation for the negative endoluminal samples. DOTATATE PET/CT at six months showed no abnormal uptake, and the patient remains recurrence-free at eight months. This case highlights the diagnostic challenge of primary hilar biliary NETs and the limitations of superficial endoluminal sampling.

Categories: General Surgery, Gastroenterology
Keywords: bile duct, hepatectomy, hepatic duct, neuroendocrine tumor, perihilar cholangiocarcinoma

Introduction

Neoplasms of the biliary tract are uncommon, with cholangiocarcinoma (CCA) representing the predominant malignant histology. In contrast, primary biliary neuroendocrine tumors (PBilNETs) are exceptionally rare, accounting for approximately 0.2-2% of gastroenteropancreatic neuroendocrine neoplasms and less than 1% of primary biliary malignancies. Accordingly, current knowledge is derived mainly from isolated case reports and small case series [1,2]. The pathogenesis of PBilNETs remains ill-determined. Neuroendocrine cells are only sparsely distributed within the biliary epithelium, and proposed mechanisms include neuroendocrine differentiation arising in chronically inflamed or metaplastic epithelium and origin from multipotent epithelial progenitor cells [1,2].

Clinically, PBilNETs usually present with manifestations related to biliary obstruction, while radiological findings are nonspecific and frequently overlap with those of CCA [1]. This diagnostic difficulty is particularly relevant for tumors arising at the hepatic hilum or common hepatic duct, where well-differentiated NETs have been reported, including lesions initially considered perihilar CCA (pCCA) [3-6]. In the recent systematic review by Paspala et al., only 12 of 54 patients with a reported preoperative diagnosis were correctly recognized as having a NET, whereas 24 of 54 were considered to have pCCA [1]. Tissue acquisition may also be inconclusive because these tumors can grow predominantly within or beneath the ductal wall, limiting the yield of superficial endoluminal sampling [1]. We herein report the case of a well-differentiated grade 2 NET of the right and common hepatic ducts that was managed as presumed pCCA despite negative forceps biopsy and brush cytology.

Case Presentation

A 73-year-old Caucasian woman with a history of cholecystectomy presented to our department with nonspecific abdominal discomfort. Preoperative laboratory investigations revealed a cholestatic biochemical pattern, with a total bilirubin level of 0.9 mg/dL, aspartate aminotransferase (AST) of 48 U/L, alanine aminotransferase (ALT) of 62 U/L, alkaline phosphatase (ALP) of 285 U/L, and gamma-glutamyl transferase (GGT) of 310 U/L. Initial abdominal ultrasonography (US) demonstrated biliary dilatation, and serum carbohydrate antigen 19-9 (CA19-9) was elevated at 230 U/mL (reference range: 0-37 U/mL).

Magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) demonstrated an infiltrative lesion centered at the hepatic duct confluence, measuring approximately 4.0 x 3.1 x 3.0 cm. The lesion caused almost complete obstruction of the right hepatic duct and stenosis with partial obstruction of the left hepatic duct, with mild heterogeneous enhancement and diffusion restriction.

Endoscopic ultrasonography (EUS) showed a firm hyperechoic lesion at the hepatic hilum adjacent to the biliary bifurcation, measuring approximately 4.4 x 3.0 cm, with small internal anechoic areas and dilatation of the central biliary tree. The endosonographic appearance resembled pCCA. Endoscopic retrograde cholangiopancreatography (ERCP) performed the same day failed to opacify the left hepatic duct and demonstrated abrupt interruption and deformity of the right hepatic duct near the common hepatic duct bifurcation. Forceps biopsies were obtained from the stenosis and brush cytology was performed. The biopsy showed fibrosclerotic bile duct tissue with mild lymphocytic inflammation and no atypia, dysplasia, or malignancy. Brush cytology was likewise negative for malignancy.

Contrast-enhanced computed tomography (CT) confirmed marked right-sided and milder left-sided intrahepatic biliary dilatation. A 3.6-cm soft-tissue mass was centered at the confluence of the right and left hepatic ducts and extended toward the confluence of the right anterior and posterior sectoral ducts. A thin cleavage plane was preserved between the lesion and the right hepatic artery (Figure *1A*). The lesion abutted the portal vein bifurcation and mildly compressed the right portal vein, with approximately 180° of contact (Figure *1B*). No definite metastatic disease was identified. Preoperative 18F-fluorodeoxyglucose PET/CT showed no appreciable FDG uptake within the hilar lesion. Nevertheless, the combined anatomical findings remained highly suspicious for pCCA. Following multidisciplinary discussion, a decision for curative-intent surgery was made.

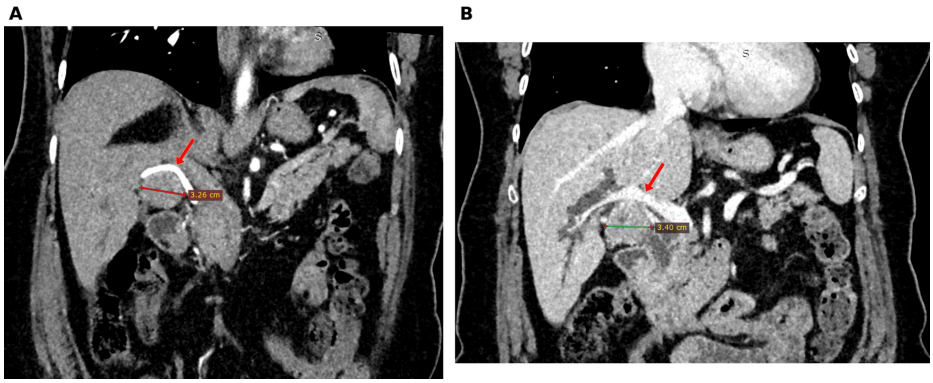


FIGURE 1: Contrast-enhanced computed tomography demonstrating the relationship of the perihilar mass with the hilar vasculature

(A) The right hepatic artery (arrow) courses adjacent to the lesion, with a preserved cleavage plane and no radiological evidence of arterial invasion. (B) The lesion abuts and mildly compresses the right portal vein (arrow), with approximately 180° of contact

Accordingly, the patient underwent right hepatectomy with en bloc extrahepatic bile duct resection and comprehensive regional lymphadenectomy of the hepatic hilum, including removal of lymphatic tissue surrounding the portal vein, hepatic artery, and extrahepatic bile duct within the hepatoduodenal ligament, followed by Roux-en-Y hepaticojejunostomy to the left hepatic duct. Caudate lobectomy was not performed, as preoperative imaging showed no evidence of tumor extension toward the caudate lobe. No vascular resection or reconstruction was required, and the bile duct transection levels were determined based on intraoperative macroscopic assessment of the extent of the lesion, without frozen-section examination of the resection margins. The postoperative course was complicated by a pleural effusion that was successfully treated by thoracentesis. The patient was discharged after a 12-day hospital stay.

Gross examination of the resected specimen demonstrated a 4.3 x 3.0 x 2.8 cm tumor involving the walls of the right and common hepatic ducts. The neoplasm occupied the full thickness of the involved ductal wall, with focal extension into the surrounding hilar connective and adipose tissue, but without hepatic parenchymal invasion. Vascular tumor emboli were present. In substantial areas, the biliary epithelium remained preserved and was separated from the underlying tumor by fibrous tissue. Microscopically, the tumor showed well-differentiated neuroendocrine morphology with nested and organoid growth and characteristic salt-and-pepper chromatin. Immunohistochemistry showed diffuse positivity for synaptophysin, CD56, and insulinoma-associated protein 1 (INSM1), whereas chromogranin was negative. The Ki-67 proliferation index was 5%, establishing the diagnosis of a well-differentiated neuroendocrine tumor, grade 2. The common bile duct, left hepatic duct, and hepatic parenchymal margins were negative, and all four examined regional lymph nodes were free of metastases, confirming an R0, node-negative

resection.

Following multidisciplinary review by oncology and endocrinology, surveillance without adjuvant treatment was recommended. At six months after surgery, DOTATATE PET/CT showed no abnormal somatostatin receptor-avid lesion. At eight months after resection, the patient remains in good general condition without evidence of recurrence.

Discussion

The present case illustrates the difficulty of distinguishing a PBilNET from pCCA prior to surgery. MRI/MRCP, EUS, ERCP, and CT consistently demonstrated a hilar mass with predominantly right-sided biliary obstruction, while its relationship with the portal bifurcation and the elevated CA19-9 level reinforced suspicion of CCA. Nevertheless, these findings established the anatomical location and extent of the lesion rather than its histological identity. In our recent systematic review, only 12 of 54 patients with a reported preoperative diagnosis were correctly identified as having a PBilNET, whereas 24 were considered to have a pCCA [1]. Notably, the absence of appreciable FDG uptake in our patient did not resolve this diagnostic uncertainty.

Several features of this case also demonstrate the variability of PBilNET presentation. The patient's age of 73 years and tumor diameter of 43 mm exceeded the median values of 49 years and 22 mm reported in our systematic review, whereas the hilar location corresponded to the most frequently involved site, accounting for 32 of 64 patients with available anatomical data [1]. Although CA19-9 elevation strengthened the initial suspicion of CCA, elevated values were also documented in 11 of 40 patients with PBilNETs in whom this marker was reported [1]. These observations indicate that neither advanced age nor elevated CA19-9 excludes a well-differentiated PBilNET. Previous reports of common hepatic duct and hilar NETs similarly describe lesions initially interpreted as CCA [3-6].

The most instructive finding was the discrepancy between the suspicious imaging appearance and the negative ERCP-directed forceps biopsy and brush cytology. Examination of the resection specimen demonstrated predominantly intramural growth, with substantial preservation of the overlying biliary epithelium and intervening fibrous tissue. This provides a plausible anatomical explanation for the failure of superficial endoluminal sampling to obtain representative tumor cells. Our systematic review likewise identified subepithelial growth and limitations of endoscopic sampling as potential contributors to inconclusive preoperative tissue diagnosis [1]. Nevertheless, preoperative identification is possible when adequate material is obtained, as illustrated by Choi et al., who diagnosed a common hepatic duct NET G2 using brush cytology and neuroendocrine immunocytochemistry [7].

Peroral cholangioscopy with targeted biopsies may improve diagnostic accuracy in patients with indeterminate biliary strictures by allowing direct visualization and targeted tissue sampling. However, its diagnostic yield may remain limited in predominantly intramural lesions with preserved overlying biliary epithelium, as superficial biopsies may fail to capture the underlying tumor [1]. In our patient, the highly suspicious imaging findings and elevated CA19-9 level supported surgical management despite negative ERCP-directed tissue sampling. Although cholangioscopy was not performed, additional targeted biopsies might have provided further diagnostic information; nevertheless, a negative result would not have reliably excluded malignancy or necessarily altered the indication for surgical resection.

Definitive diagnosis in our case depended on the integration of morphology, immunophenotype, and proliferative activity. The organoid architecture and characteristic nuclear features, together with diffuse synaptophysin, CD56, and INSM1 expression and a Ki-67 index of 5%, supported classification as a well-differentiated NET G2 despite negative chromogranin staining [2,8]. Establishing a primary biliary origin additionally requires consideration of an alternative primary NET [1,2]. Somatostatin receptor PET/CT can assist whole-body staging of well-differentiated NETs [9]; in our patient, postoperative DOTATATE PET/CT showed no abnormal receptor-avid lesion.

The primary biliary origin of the tumor was further supported by its location within the walls of the right and common hepatic ducts and the absence of an identifiable extrabiliary primary lesion on preoperative cross-sectional imaging. In particular, no suspicious pancreatic or gastrointestinal primary tumor was identified. Although postoperative DOTATATE PET/CT revealed no abnormal receptor-avid lesions, an occult extrabiliary primary cannot be excluded with absolute certainty. Nevertheless, the combined anatomical, histopathological, and imaging findings strongly favored a primary biliary neuroendocrine tumor.

Complete surgical (R0) resection with negative margins remains the gold standard treatment for localized PBilNET, with the operative extent dictated by tumor location and anatomical involvement [1]. In our patient, right-sided hilar extension and the presumed diagnosis of pCCA prompted right hepatectomy with en bloc extrahepatic bile duct resection and regional lymphadenectomy, achieving an R0, node-negative resection without vascular reconstruction. The procedures described in our systematic review ranged from isolated bile duct excision with biliary reconstruction to pancreaticoduodenectomy or hepatectomy, reflecting the different anatomical requirements for complete tumor clearance [1]. Following definitive

pathological diagnosis, the absence of an established benefit from adjuvant therapy after complete resection of well-differentiated PBilNET supported the multidisciplinary decision to pursue surveillance [1]. Adjuvant treatment has occasionally been administered following resection of PBilNETs; nonetheless, the small number of treated patients and incomplete reporting of treatment indications and regimens preclude solid conclusions regarding their oncological benefit.

The postoperative findings are encouraging but do not establish long-term oncological control. Well-differentiated morphology, a relatively low Ki-67 index, R0 resection, and absence of nodal metastases were favorable features, whereas vascular tumor emboli and focal extension into surrounding hilar tissue warrant caution. Our systematic review identified hepatic recurrence in three of 51 patients with reported follow-up, but the median follow-up of 19 months, incomplete reporting, and selection of surgically treated patients limit interpretation of this proportion [1]. Miyashita et al. also described delayed and repeated hepatic recurrence after resection of a PBilNET G2, requiring successive hepatectomies [10]. Accordingly, the negative DOTATATE PET/CT at six months and absence of recurrence at eight months in our patient support a favorable early outcome while emphasizing the need for prolonged surveillance.

This case reinforces the importance of considering PBilNET in the differential diagnosis of a hilar mass, particularly when imaging suggests CCA yet endoluminal tissue sampling may be inconclusive. Its principal contribution is the pathological demonstration of an intramural tumor beneath preserved biliary epithelium, which helps explain the diagnostic limitations encountered before surgery. Accurate classification and individualized postoperative management require close collaboration among hepatobiliary surgeons, pathologists, oncologists, endocrinologists, and nuclear medicine specialists to pursue the optimal outcomes for patients.

Conclusions

Primary biliary neuroendocrine tumors pose important diagnostic and therapeutic challenges due to their rarity and resemblance to CCA. Awareness of this diagnostic possibility, careful interpretation of inconclusive biopsy results, and multidisciplinary decision-making are essential to guide appropriate management. Given the limited evidence regarding long-term outcomes, individualized surveillance remains important.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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