

## CASE STUDY

# Novel Neuroendocrine Tumor in Multiple Endocrine Neoplasia Type 1

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This case highlights the appropriate use of genetic testing and supports expanding the clinical diagnosis of multiple endocrine neoplasia type 1 to include neuroendocrine tumors of the extrahepatic bile duct.

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Neuroendocrine tumors (NETs) are uncommon and can occur in the context of genetic conditions. Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant disorder of the tumor suppressor gene of the same name—*MEN1*, which encodes for the protein menin. Multiple endocrine neoplasia type 1 is characterized clinically by the presence of 2 or more of the following NETs: parathyroid, pituitary, and pancreaticoduodenal.<sup>1</sup> Pancreaticoduodenal NETs occur in 30% to 80% of patients with MEN1 and have malignant potential. Although the majority of pancreaticoduodenal NETs are nonfunctioning, patients may present with symptoms secondary to mass effect.

Genetic testing exists for MEN1, but not all genetic mutations that cause MEN1 have been discovered. Therefore, because negative genetic testing does not rule out MEN1, a diagnosis is based on tumor type and location. Neuroendocrine tumors of the biliary tree are rare, and there are no well-accepted guidelines on how to stage them.<sup>2-4</sup> The following case demonstrates an unusual initial presentation of a NET in the context of MEN1.

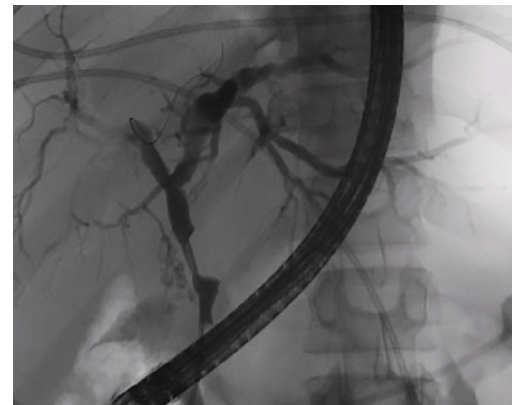
### CASE REPORT

A 29-year-old, active-duty African-American man deployed in Kuwait presented with icterus, flank pain, and hematuria. His past medical history was significant for nephrolithiasis, and his family history was notable for hyperparathyroidism. Laboratory results showed primary hyperparathyroidism and evidence of biliary obstruction.

A sestamibi scan demonstrated uptake in a location corresponding with the right inferior parathyroid gland. A computed tomography (CT)

scan showed nephrolithiasis and hepatic biliary ductal dilatation. Magnetic resonance cholangiopancreatography (MRCP) revealed both intra- and extrahepatic ductal dilatation, focal narrowing of the proximal common bile duct, and possible adenopathy that was concerning for cholangiocarcinoma. Endoscopic retrograde cholangiopancreatography (ERCP) demonstrated a 1 cm to 2 cm focal stricture within the mid-common bile duct with intra- and extrahepatic ductal dilatation (Figure 1). An endoscopy showed no masses in the duodenum, and an endoscopic ultrasound showed no masses in the pancreas. Endoscopic brushings and endoscopic, ultrasound-guided, fine-needle aspiration cytology were nondiagnostic. Exploratory laparotomy revealed a dilated hepatic bile duct, an inflamed porta hepatis, and a mass involving the distal hepatic bile duct.

**FIGURE 1**  
Endoscopic Retrograde Cholangiopancreatography



Endoscopic retrograde cholangiopancreatography revealing stricture in mid-common bile duct.

The patient underwent cholecystectomy, radical extra hepatic bile duct resection to the level of the hepatic bifurcation, and hepaticojejunostomy. Gross examination of the specimen showed a nodule centered in the distal common hepatic duct with an adjacent, 2-cm lymph node. The histologic examination revealed a neoplastic proliferation consisting of epithelioid cells with round nuclei and granular chromatin with amphophilic cytoplasm in a trabecular and nested architecture.

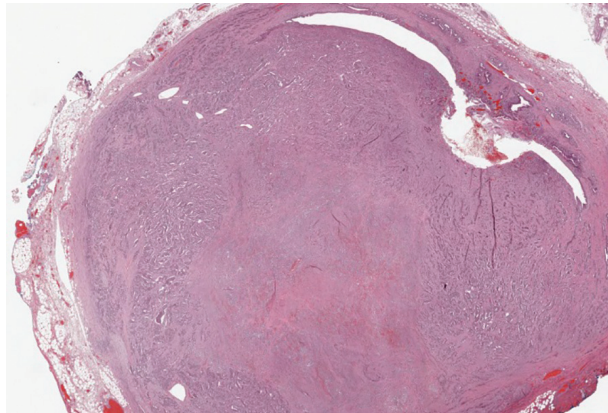
The tumor was centered in the submucosa, which is typical of gastrointestinal NETs (Figure 2). There was no evidence of direct tumor extension elsewhere. About 40% of the tumor cells contained eosinophilic, intracytoplasmic inclusions (Figure 3). The tumor did not involve the margins or lymph node.

Positive staining with the neuroendocrine markers synaptophysin and chromogranin A confirmed a well-differentiated NET. The intracytoplasmic inclusions stained strongly positive for cytokeratin CAM 5.2. The tumor had higher-grade features, including tumor cell necrosis, a Ki-67 labeling index of 3%, and perineural invasion. The 2010 World Health Organization (WHO) criteria for NET of the digestive system classified this tumor as a grade 2, well-differentiated NET and as stage 1a (limited to the bile duct).<sup>4</sup>

Postoperatively, octreotide scan with single-photon emission computed tomography (SPECT)-CT did not show additional masses or lesions. Serum pancreatic polypeptide was elevated, with the remaining serum and plasma NET markers—including gastrin, glucagon, insulin, chromogranin A, and vasoactive intestinal polypeptide (VIP)—being within reference ranges. Genetic testing (GeneDx, Inc, Gaithersburg, MD) showed an E563X nonsense mutation in the *MEN1* gene, confirming a *MEN1* disorder. The patient then underwent a 4-gland parathyroidectomy with reimplantation; the parathyroid glands demonstrated hyperplasia in all 4 glands.

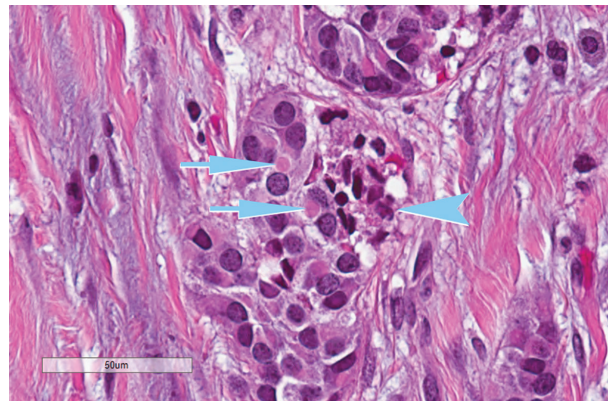
Biochemical follow-up at 14 months showed that the serum pancreatic polypeptide had normalized. There was no evidence of pituitary or pancreatic hypersecretion. The patient developed hypoparathyroidism, requiring calcium and calcitriol supplementation. Radiographic follow-up using abdominal magnetic resonance imaging at 16 months showed no evidence of disease.

**FIGURE 2**  
**Low-Power Image of Nodule and Bile Duct Epithelium**



Hematoxylin and eosin stain, 10x magnification.

**FIGURE 3**  
**Tumor Cell With Eosinophilic Intracytoplasmic Inclusions**



A subset of the tumor with tumor cell necrosis (arrow head) and eosinophilic intraplastic inclusion (arrows: hematoxylin and eosin stain, 400x magnification).

## DISCUSSION

This case illustrates a genetic disease with an unusual initial presentation. Primary extrahepatic bile duct NETs are rare and have been reported previously in patients without *MEN1*.<sup>5-9</sup> Neuroendocrine tumors in the hepatic bile duct in patients with *MEN1* also have been reported but only after these tumors first appeared in the pancreas or duodenum.<sup>10</sup> An extensive literature search revealed no prior reports extrahepatic bile duct NETs with *MEN1* as the primary site or with biliary obstruction, which is why this patient's presentation is particularly interesting.<sup>5,6,10-13</sup> The table summarizes select reports of NETs.

**TABLE**  
**Literature Review of Select NETs**

Study	Tumor Location	Hormone Production	MEN1	Inclusions
Price et al, 2009 <sup>5</sup>	Pancreas, liver, and extrahepatic biliary tree	Gastrin	+	
	Pancreas, duodenum, common bile duct, stomach, lymph nodes	Gastrin	+	
	Liver, bone, lymph node	Gastrin		
Bhandarwar et al, 2012 <sup>9</sup>	Extrahepatic biliary tree			
Gibril et al, 2004 <sup>11</sup>	Pancreas ± liver or bone	Gastrin ± insulin	+	
Pipeleers-Marichal et al, 1990 <sup>13</sup>	Duodenum ± pancreas, liver and/or lymph nodes	Gastrin or insulin	+	
Serra et al, 2006 <sup>17</sup>	Pancreas ± liver or lymph nodes	Pancreatic polypeptide, insulin, VIP, somatostatin, glucagon, gastrin		+
	Pancreas ± lymph nodes	Gastrin, glucagon, insulin, VIP, somatostatin	+	+
Shia et al, 2004 <sup>18</sup>	Pancreas, liver			+
Perez-Montiel et al, 2003 <sup>19</sup>	Pancreas ± liver or lymph nodes	Gastrin		+

Abbreviations: NETs, neuroendocrine tumors; MEN1, multiple endocrine neoplasia type 1; VIP, vasoactive intestinal polypeptide.

Tumor location in this patient was atypical, and genetic testing guided the management. Serum MEN1 genetic testing is indicated in patients with ≥ 2 tumors that are atypical but possibly associated with MEN1 (such as adrenal tumors, gastrinomas, and carcinoids) and in patients aged < 45 years with primary hyperparathyroidism.<sup>14,15</sup> The patient in this study was aged 29 years and had hyperparathyroidism and an NET of the hepatic bile duct. This condition was sufficient to warrant genetic testing, the results of which affected the patient's subsequent parathyroid surgery.<sup>15</sup> Despite the suggestion of unifocal localization on the sestamibi scan, the patient underwent the more appropriate subtotal parathyroidectomy.<sup>14</sup> The patient's tumor most likely originated from a

germline mutation of the *MEN1* gene.

As a result of the patient's genetic test results, his daughter also was tested. She was found to have the same mutation as her father and will undergo proper tumor surveillance for MEN1. There was no personal or family history of hemangioblastomas, renal cell carcinomas, or cystadenomas, which would have prompted testing for von Hippel-Lindau disease. Likewise, there was no personal or family history of café-au-lait macules and neurofibromas, which would have prompted testing for neurofibromatosis type 1.

Due to the paucity of cases, there are currently no well-accepted guidelines on how to stage extrahepatic biliary NETs.<sup>3-5,16</sup> The WHO recommends staging according to adenocarcinomas of the gallbladder and bile duct.<sup>3</sup> As such, the pathologic stage of this tumor would be stage 1a.

The significance of the intracytoplasmic inclusion in this case is unknown. Pancreatic NETs and neuroendocrine carcinomas have demonstrated intracytoplasmic inclusions that stain positively for keratin and may indicate more aggressive tumor behavior.<sup>17-19</sup> In 1 report, electron microscopic examination demonstrated intermediate filaments with entrapped neurosecretory granules.<sup>18</sup> In a series of 84 cases of pancreatic endocrine tumors, 14 had intracytoplasmic inclusions; of these, 5 had MEN1.<sup>17</sup> In the present case, the patient continues to show no evidence of tumor recurrence at 16 months after resection.

**CONCLUSION**

Extrahepatic biliary neuroendocrine tumors are rare. Further investigation into biliary tree NET staging and future studies to determine the significance of intracytoplasmic inclusions may be beneficial. This case highlights the appropriate use of genetic testing and supports expanding the clinical diagnosis of MEN1 to include NETs of the extrahepatic bile duct.

**AUTHOR DISCLOSURES**

*The authors report no actual or potential conflicts of interest with regard to this article.*

**DISCLAIMER**

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