ACG CASE REPORTS JOURNAL

CASE REPORT | PATHOLOGY

Endoscopic Ultrasound-Guided Diagnosis of Gallbladder Mixed Neuroendocrine Non-Neuroendocrine Tumor With an Anomalous Pancreaticobiliary Junction

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ABSTRACT

Mixed neuroendocrine non-neuroendocrine neoplasms are exceedingly rare tumors, especially those of gallbladder origin. Anomalous pancreaticobiliary junction is an uncommon congenital abnormality that can predispose various types of hepatobiliary malignancies. We present an unusual case of a 46-year-old woman with anomalous pancreaticobiliary junction who presented to the emergency department with nausea, vomiting, and right upper quadrant pain. Magnetic resonance imaging revealed a gallbladder mass concerning for primary malignancy and liver lesions. Endoscopic ultrasound and fine-needle biopsy were valuable diagnostic tools used to sample the gallbladder, liver lesions, and common hepatic duct under one minimally invasive procedure. Pathology showed a gallbladder mixed neuroendocrine non-neuroendocrine neoplasms, with neuroendocrine components in the liver and adenocarcinoma components in the common hepatic duct.

KEYWORDS: neuroendocrine tumor; mixed tumor; anomalous pancreaticobiliary junction; endoscopic ultrasound

INTRODUCTION

Mixed neuroendocrine non-neuroendocrine neoplasms (MiNENs) are a pathologically heterogenous group of tumors defined by the World Health Organization as mixed neoplasms of gastroenterohepatic origin with neuroendocrine and non-neuroendocrine components. These are a rare form of gallbladder malignancy.[1,2] The majority of literature on gallbladder MiNEN stems from case reports making true incidence unknown, but the 2008 Surveillance of Rare Cancers in Europe registry approximates MiNEN incidence as $<$0.01/100,000 cases per year.[2] An anomalous pancreaticobiliary junction (APBJ) is a rare congenital malformation associated with hepatobiliary and pancreatic disorders such as choledochal cysts, choledocholithiasis, gallbladder carcinoma, cholangiocarcinoma, and recurrent pancreatitis.[3] It is estimated that approximately 10% of patients with APBJ will develop gallbladder carcinoma over the course of their lifetime.[3,4] We present an unusual case of a gallbladder mass with liver lesions and common hepatic duct (CHD) stricture with subsequent endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography sampling which revealed MiNEN with metastatic neuroendocrine tumors in the liver and adenocarcinoma in the CHD in a patient with an APBJ.

CASE REPORT

A 42-year-old African American woman with a history of type 2 diabetes mellitus and hypertension presented to the emergency department with 1-month history of worsening nausea, vomiting, right upper quadrant abdominal pain, and 10 pounds of unintentional weight loss. Liver function tests were elevated: aspartate aminotransferase 430 U/L, alanine aminotransferase 575 U/L, alkaline phosphatase 459 U/L, and total bilirubin 1.7 mg/dL. Tumor markers were sent and notable for elevation of both

ACG Case Rep J 2024;11:e01566. doi:10.14309/crj.0000000000001566. Published online: December 4, 2024

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carcinoembryonic antigen (225 ng/mL) and CA19-9 (183.9 U/mL). Magnetic resonance imaging of the abdomen and pelvis revealed an enhancing nodular mass at the fundus of the gallbladder concerning for primary malignancy (Figure 1). Also noted were multifocal liver lesions, infiltration of the porta hepatis, and necrotic retroperitoneal lymph nodes concerning for metastatic disease (Figure 1). Magnetic resonance cholangiopancreatography (MRCP) confirmed the gallbladder mass in addition to a biliary stricture (Figure 1).

EUS and endoscopic retrograde cholangiopancreatography were subsequently performed. EUS demonstrated a 20 mm × 15 mm heterogenous, hypoechoic mass in the neck of the gallbladder with irregular outer margins and likely invasion of the hepatic parenchyma. The right lobe of the liver contained round, homogenous, and hyperechoic lesions suggestive of metastases, with the largest measuring 8 mm (Figure 2). Fine-needle biopsy was performed for both the gallbladder and hepatic masses (Figure 2). Cholangiogram was notable for a 1 cm stricture in the CHD and a Komi classification type IIA APBJ. Cholangioscopy performed revealed narrowing at the CHD and associated erythema, congestion, and increased vascularization concerning for malignant stricture. Biopsies were taken from the CHD for pathology, and brushings were obtained for cytology. A plastic biliary stent was placed in the common bile duct at the end of the procedure.

Pathology revealed 2 unique populations of tumor cells (Figure 3). This confirmed the diagnosis of a MiNEN in the gallbladder, with neuroendocrine tumors in the liver, and adenocarcinoma in the CHD. The patient has started chemotherapy with carboplatin and etoposide.

DISCUSSION

APBJ is a rare congenital malformation wherein the pancreatic and bile ducts join to form a common channel outside of the duodenal wall. The reflux of pancreatic enzymes into the biliary tract causes increased hyperplastic changes in the gallbladder and bile duct, and markedly increases rates of malignancy, predominantly adenocarcinoma.[3,5–7] This also explains why APBJ is an independent risk factor of gallbladder malignancy

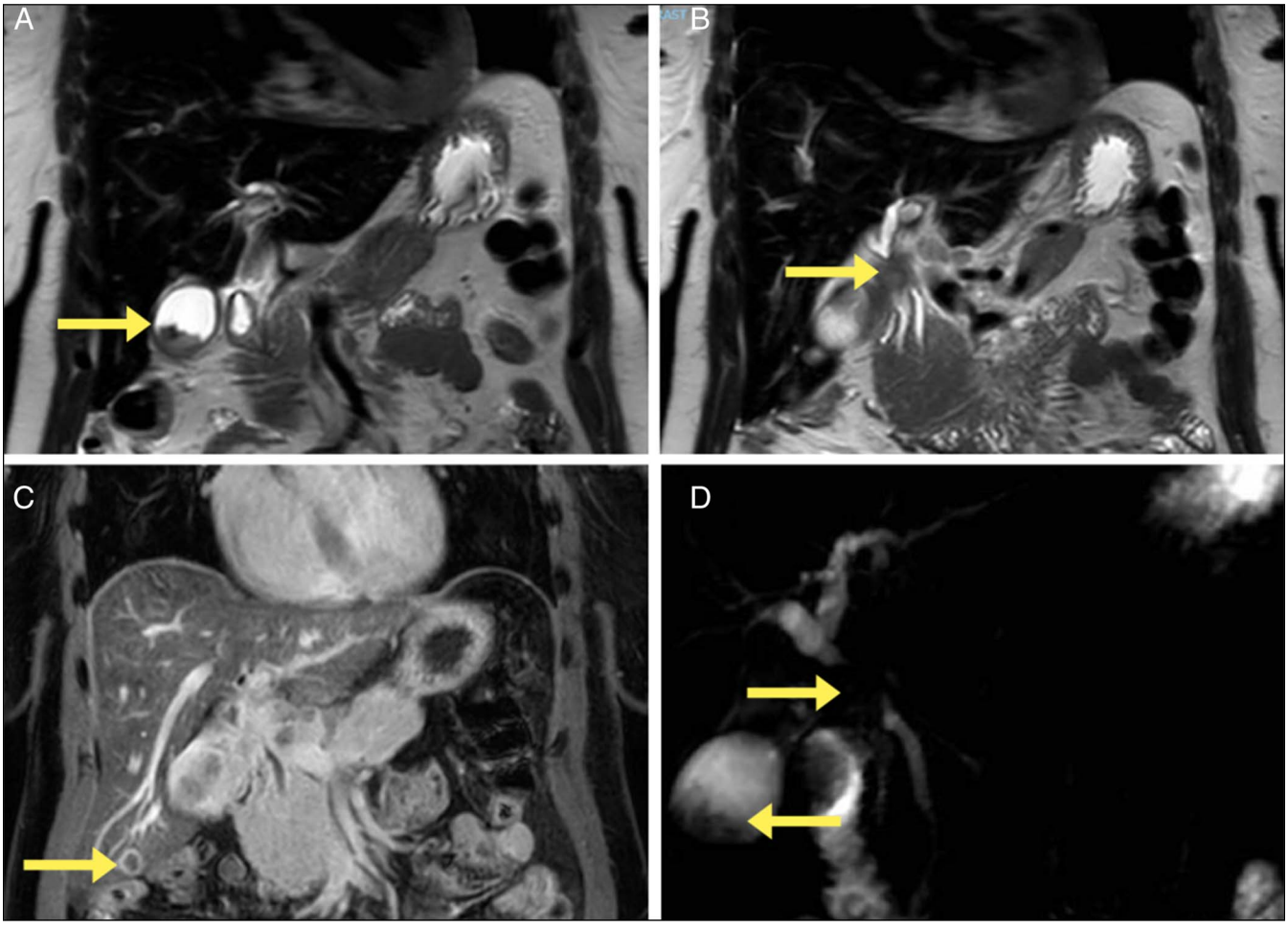

Figure 1. (A) Coronal MRI highlighting gallbladder mass (arrow). (B) Coronal MRI highlighting biliary stricture (arrow). (C) Coronal MRI demonstrating liver mass (arrow). (D) Magnetic resonance cholangiopancreatography sequence with both mass and stricture. MRI, magnetic resonance imaging.

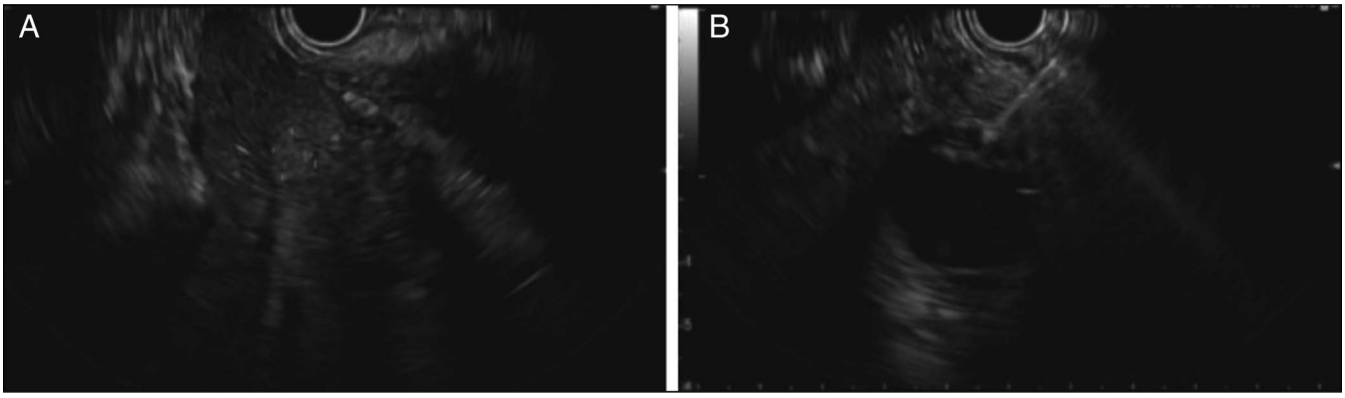

Figure 2. (A) EUS imaging of liver lesion in the right lobe. (B) EUS-guided fine-needle biopsy of gallbladder mass. EUS, endoscopic ultrasound.

due to the development of precursor neuroendocrine metaplasia from chronic inflammation.[4] Prophylactic cholecystectomy is recommended for patients with APBJ to prevent the onset of malignant changes even without choledochal cyst.[5,8] Rates of gallbladder malignancy from a nationwide survey in Japan ranged from 21.6% to as high as 42.4% in patients with dilated and non-dilated-type APBJ, respectively.[5,9] This pathophysiology may have played a role in the development of our patient's gallbladder, liver, and CHD malignancies. APBJ-associated gallbladder carcinomas are also documented more

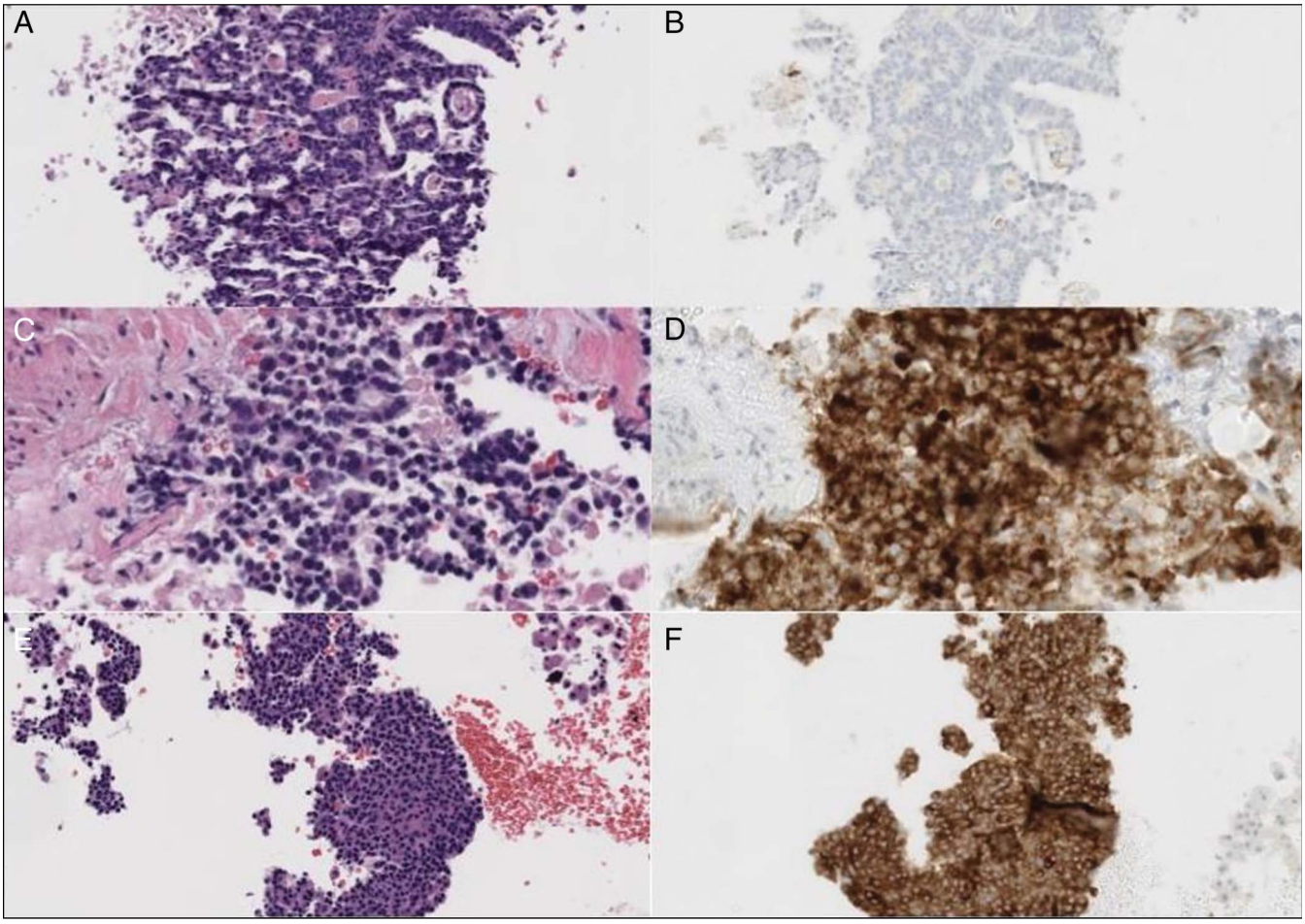

Figure 3. Histologic slides of biopsy from gallbladder tumor and liver metastasis. The image shows (A) 20× H&E stain showing adenocarcinoma component of the gallbladder tumor, (B) synaptophysin stain negative in the adenocarcinoma component, (C) 40× H&E stain showing neuroendocrine neoplasm component of the gallbladder tumor, (D) strongly positive synaptophysin stain in the neuroendocrine neoplasm component of the gallbladder tumor, (E) the liver metastasis with purely neuroendocrine neoplasm, (F) strongly positive synaptophysin stain in liver metastasis. H&E, hematoxylin and eosin.

often in younger, female patients compared with non-APBJ-associated cases.[3]

Even more unusual are MiNENs arising in the setting of an APBJ, especially those that are of gallbladder origin. Although neuroendocrine differentiation of APBJ-associated tumors are not well documented, this case is consistent with previously reported demographics of APBJ-associated gallbladder carcinomas. The neuroendocrine components of MiNENs tend to display more aggressive behavior than non-neuroendocrine components and have a higher likelihood for metastasis.[10,11] Neuroendocrine tumors of pancreaticobiliary origin most commonly metastasize to the liver, which is associated with a worse prognosis.[12]

In diagnosing a MiNEN, immunohistochemical testing is imperative. Mucicarmine is highly specific for glandular epithelial mucin found in adenocarcinoma, and chromogranin and synaptophysin identify secretory vesicles seen in neuroendocrine tumors.[13,14] In this case, immunohistochemistry determined 2 unique tumor cell differentiations in the gallbladder lesion. One component stained positive for mucicarmine and negative for synaptophysin, indicating mucinous adenocarcinoma (Figure 3). CAM5.2, CDX2, CK7 (patchy), and CK20 (patchy) were positive, suggesting primary gastrointestinal origin.[15–17] The same morphology was found in the CHD stricture biopsy.

In the other component of the gallbladder lesion, positive chromogranin, synaptophysin, CAM5.2, CK7, CK20, and CDX2 (patchy) staining confirmed neuroendocrine differentiation of gastrointestinal origin (Figure 3).[15–17] Tumor cells in the liver stained positive for CK7, CK20, PAX8, chromogranin, and synaptophysin, also confirming neuroendocrine differentiation (Figure 3). This similar morphology determined the presence of a metastatic high-grade neuroendocrine neoplasm from the gallbladder. Ki-67 immunostaining of the neuroendocrine component in both the gallbladder and liver lesion showed more than 60% of cells with mitotic activity, indicative of a highly proliferative neuroendocrine neoplasm which correlates with a more aggressive clinical course.[18]

Treatment recommendations for MiNENs follow standard of care for either neuroendocrine or adenocarcinoma components, but most cases target treatment against the neuroendocrine component due to often more aggressive behavior and poorer prognosis.[2,19,20] Platinum-etoposide chemotherapy is recommended for gastrointestinal neuroendocrine tumors.[21,22]

This case illustrates the value of endoscopic ultrasound-guided sampling as a minimally invasive, nonoperative approach in evaluating multiple hepatobiliary tract lesions in a single procedure, thereby minimizing complications and aiding in timely diagnosis.[23,24] It is imperative in sampling multiple areas where lesions may be to confirm a more accurate diagnosis.

DISCLOSURES

Author contributions: E. Holzwanger performed the procedures. E. Tsuchiyose drafted the manuscript. M. Talanian and E. Holzwanger revised and reviewed the manuscript. H. Liao reviewed the pathology sections and prepared the pathology figure and legend. E. Holzwanger is the article guarantor.

Financial disclosure: E. Holzwanger is a medical consultant for Boston Scientific. The remainder of authors have no conflicts of interest.

Informed consent was obtained for this case report.

Received September 15, 2024; Accepted November 7, 2024

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