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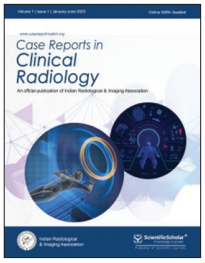

Case Report

Unusual case of biliary neuroendocrine tumor

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ABSTRACT

This case report showcases the imaging findings in a patient with a biliary neuroendocrine tumor (NET). NETs encompass a wide variety of diseases and comprise neoplasms arising from neural crest tissues during embryonic development. NETs can be found in different organs, including the gastrointestinal tract, adrenal medulla, pituitary gland, hypothalamus, and thyroid gland. Biliary NETs are uncommon and makeup <1% of all NETs.

Keywords: Neuroendocrine tumor, Biliary tract, Common hepatic duct, Obstructive jaundice

INTRODUCTION

Neuroendocrine tumors (NETs) affecting the extrahepatic bile ducts are extremely uncommon, with limited documented cases in the literature since Pilz initially described this condition in 1961. Biliary NETs often present with obstructive jaundice. They are commonly misdiagnosed as cholangiocarcinoma due to their similar clinical presentation. This case report showcases the imaging findings of a neuroendocrine tumor in the common hepatic duct in a patient presenting with obstructive jaundice.

CASE REPORT

In our case, a 33-year-old male with no known comorbidities presented with complaints of upper abdominal pain and discomfort, dyspepsia, dark-colored urine, yellowish discoloration of eyes, pruritus, and clay-colored stool of 1-month duration. There is no history of fever, abdominal lump, or change in bowel habits. The patient's laboratory results showed an elevated bilirubin level and features of obstructive jaundice, with an increase in liver enzyme levels. However, the other laboratory parameters, such as complete blood count, prothrombin time, amylase, albumin, and viral markers, were found to be within normal limits.

The initial ultrasound examination [Figure 1] revealed dilatation of the intrahepatic biliary tree with a well-defined echogenic focus measuring 2.1 × 1.2 cm at the level of the hilum. This focus showed no demonstrable internal vascularity. Magnetic resonance cholangiopancreatography followed by contrast administration [Figure 2] was performed. It showed a well-defined lesion measuring 2.1 × 1.3 cm in the region of proximal common hepatic duct which was mildly hyperintense in both T1-weighted and T2-weighted images. The lesion was seen extending into the adjacent portions of the hepatic ducts (both right and left) resulting in dilation of the proximal intrahepatic biliary tree. It showed

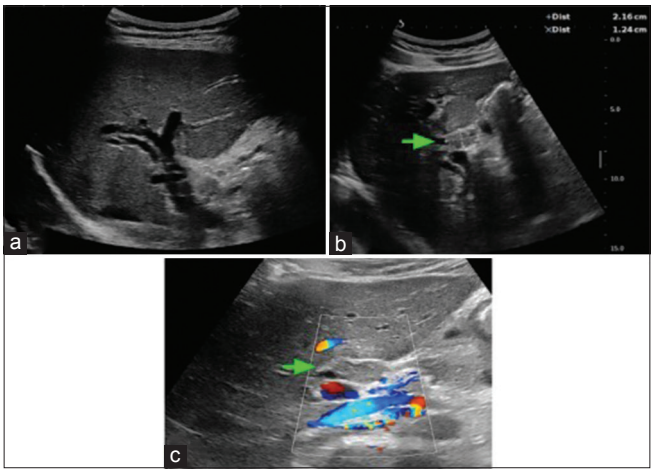

Figure 1: Ultrasound abdomen shows (a) central and peripheral biliary ductal dilation with an echogenic lesion (green arrows in b and c) (b) measuring 2.1 × 1.2 cm in the hilum showing no significant vascularity on (c) color Doppler imaging.

restricted diffusion and homogenous mild post-contrast enhancement. The cystic duct was normal and seen inserting distal to the compressing mass.

A diagnosis of cholangiocarcinoma was raised. The patient was scheduled to undergo an extended right hepatectomy. Before the surgery, the patient underwent embolization of the right portal vein to increase the size of the left lobe of the liver. In addition, transhepatic biliary drainage was performed to address the dilation of the left lobe ducts. After ensuring adequate left liver lobe volume, the patient proceeded with an extended right hepatectomy and hepaticojejunostomy. Intraoperatively, a thickened common hepatic duct extending cranially to the right hepatic duct was seen. The peritoneum, omentum, duodenum, and liver appeared normal and free of deposits.

Pathological and immunohistological examination led to a final diagnosis of grade 2 periductal infiltrating neuroendocrine with no lymphovascular infiltration. Immunohistochemical studies were positive (3+) for pan CK, chromogranin A, and synaptophysin. The Ki-67 labeling index was 10% [Figure 3]. Gallium-68 DOTANOC whole-body positron emission tomography-computed tomography (CT) scan which was done 18 months after right extended hepatectomy and hepaticojejunostomy revealed no definite evidence of somatostatin receptor (SSTR)-positive disease anywhere in the whole-body survey.

DISCUSSION

NETs encompass a diverse group of neoplasms characterized by neuroendocrine differentiation that can affect various organs. These tumors originate from embryonal neural crest cells, also known as Argentaffin or Kulchitsky cells,

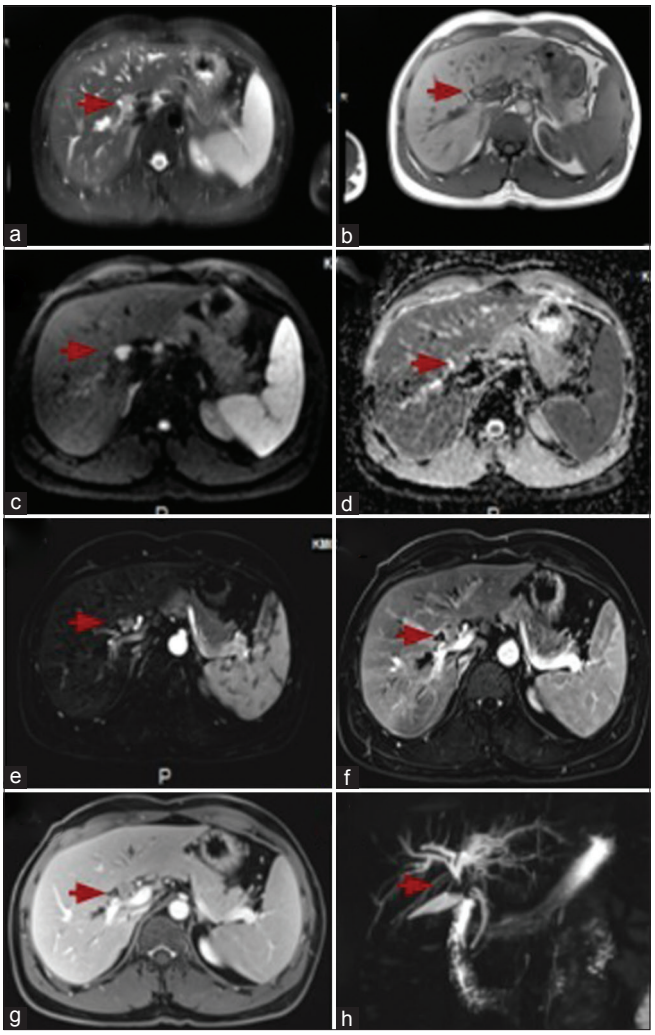

Figure 2: Magnetic resonance cholangiopancreatography (MRCP) followed by gadolinium contrast administration shows a well-defined lesion (red arrows) in the proximal common hepatic duct. The lesion appears mildly hyperintense in both (a and b) T2 and T1-weighted. Restricted diffusion is seen within the lesion in (c) diffusion-weighted imaging and (d) apparent diffusion coefficient map. On post-contrast administration, the lesion shows mild homogeneous enhancement in (e) the arterial, (f) portal venous, and (g) delayed phases. The MRCP image (h) shows that the lesion is causing upstream dilatation of central and peripheral biliary ducts.

which are prominently found in the epithelial cells of the gastrointestinal tract and the bronchopulmonary system.

NETs mostly arise in the gastrointestinal system.[1] When these tumors are functional, they are often diagnosed at an earlier stage and at a smaller size because they manifest with symptoms associated with the specific hormone they produce. On the other hand, non-functioning NETs typically grow larger and present with symptoms related to mass effect.

NETs affecting the extrahepatic bile ducts are extremely uncommon, accounting for only 0.1–0.4% of cases.[2,3] Due

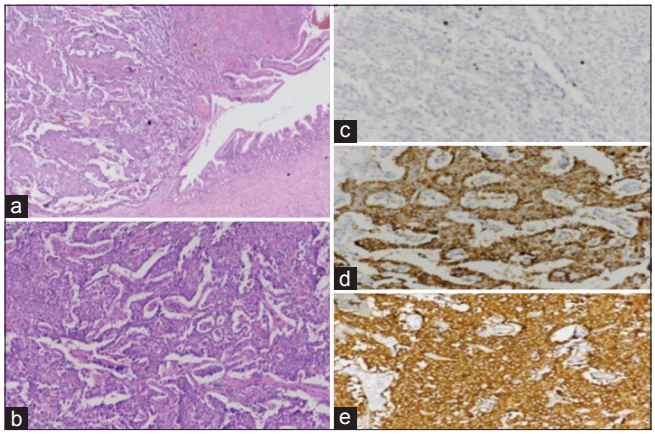

Figure 3: Photomicrograph shows the tumor with (a) adjacent normal biliary lining and (b) small round cells with scanty cytoplasm arranged in cords and trabeculae. The tumor cells had (c) Ki-67 proliferation indices of 10% and were strongly positive for (d) chromogranin A and (e) synaptophysin. (Hematoxylin-eosin stain; original magnification, ×10).

to their rarity, there are limited documented cases in the literature since Pilz initially described this condition in 1961.[4] NETs in the extrahepatic biliary tree commonly occur in the following distribution: Common bile duct (58%), perihilar region (28%), cystic duct (11%), and common hepatic duct (3%). Jaundice is the most frequently observed symptom upon presentation.[5] Pre-operative diagnosis of extrahepatic bile duct NETs is often challenging due to the absence of detectable serum markers and hormonal symptoms.[6] In comparison to NETs in other locations, endocrine tumors of the extrahepatic biliary ducts tend to exhibit a more indolent behavior.

All NETs exhibit the expression of general neuroendocrine markers, with or without the production of peptide hormones and/or biogenic amines. The presence of keratin expression distinguishes NETs from pheochromocytoma and paraganglioma, which are neuroendocrine non-epithelial neoplasms. K8 and K18 are the most commonly expressed keratins in NETs. Either or both of these can be detected using broad-spectrum keratin antibodies such as OSCAR, MAK6, AE1/AE3, and CAM5.[7] NETs, particularly well-differentiated types, typically exhibit the expression of SSTRs. SSTR functional imaging, such as Ga 68-DOTATATE, and somatostatin analog therapies, including cold peptide such as octreotide acetate, as well as peptide receptor radionuclide therapy such as Lu 177-DOTATATE, are based on the presence of somatostatin receptor subtype 2A (SSTR2A) expression.[8] Synaptophysin and chromogranin A are the commonly used traditional general neuroendocrine markers. Synaptophysin is generally considered more sensitive, while chromogranin A is considered more specific for NETs. In suspected liver metastases, along with broad-spectrum keratin immunohistochemistry, it is almost mandatory to demonstrate the positivity of general neuroendocrine markers. Both the World Health Organization (WHO) and the European Neuroendocrine Tumor Society accept the Ki-67 labeling index (LI) as a proliferative marker for NETs. The Ki-67 LI is independently correlated with survival and is considered the most reliable prognostic factor for gastroenteropancreatic NETs. According to the WHO 2010 classification, the histopathologic subtypes of NETs are as follows:

1. NET G1 and G2: These are well-differentiated NETs
2. Neuroendocrine carcinoma: This subtype is characterized by being poorly differentiated and high grade, representing a malignant neoplasm
3. Mixed adenoneuroendocrine carcinoma: This subtype exhibits a morphological phenotype that includes both epithelial and NET cells. It is classified as a carcinoma because both components are malignant in at least 30% of cases.

Various diagnostic imaging modalities, including abdominal ultrasonography, CT, and magnetic resonance imaging (MRI), can be used for biliary tumors. Gastroenteropancreatic NETs and their metastases are generally hypervascular. In CT and MRI with multiphase acquisition, these tumors are typically more conspicuous during the early arterial phase of the scan.[9] However, it is important to note that this is not universally applicable to all cases of biliary NETs. Due to the non-specific nature of radiologic findings, the definitive diagnosis is usually made post-operatively through histological and immunohistochemical examination of the surgical specimen.[10] Pre-operatively, biliary NETs are often misdiagnosed as adenocarcinoma due to their rare incidence and the similarity of their clinical presentation and non-specific radiologic findings to adenocarcinoma.[11]

DIFFERENTIAL DIAGNOSIS

The primary differential diagnosis for biliary neuroendocrine is cholangiocarcinoma. It is commonly observed as an ill-defined mass in the hilar region, leading to obstruction of the intrahepatic bile ducts, and is usually seen in elderly patients. Due to its relatively lower incidence and similar clinical presentation, biliary NETs are often misdiagnosed as cholangiocarcinoma.

Other differential diagnoses with comparable clinical and radiological features include metastasis to the biliary system, which is usually seen in elderly patients with a known primary malignancy.

IgG4-related sclerosing cholangitis, also known as autoimmune cholangiopathy, can present with a similar appearance. However, IgG4 disease may manifest with other disease manifestations such as autoimmune pancreatitis.

CONCLUSION

Biliary NETs are rare. However, in patients presenting with obstructive jaundice, biliary NETs should be kept in mind as a probable diagnosis, especially when typical risk factors for cholangiocarcinoma are not present.

TEACHING POINTS

Biliary NETs are rare and often present with obstructive jaundice. They are commonly misdiagnosed as cholangiocarcinoma due to their similar clinical presentation.

The pre-operative diagnosis of NETs is challenging due to their rarity, lack of detectable serum markers, and absence of hormonal symptoms. Definitive diagnosis typically relies on histopathological examination.

Surgical resection is currently considered the preferred treatment option to achieve a potentially curative outcome and a prolonged period of disease-free survival in patients with NETs emphasizing the importance of early diagnosis and timely intervention.

Despite their rarity, biliary NETs should be considered in the differential diagnosis of obstructive jaundice, particularly in the absence of typical risk factors for cholangiocarcinoma.

MCQs

1. Most common site of NETs in extrahepatic biliary tree is
    a. CBD
    b. Perihilar region
    c. Cystic duct
    d. Common hepatic duct

Answer Key: a

2. Functional imaging techniques for somatostatin receptors, such as Ga 68-DOTATATE based on expression of the following somatostatin receptor subtype (SSTR):
    a. SSTR 2A
    b. SSTR 1
    c. SSTR 2B
    d. SSTR 3

Answer Key: a

3. Most common presenting symptom of NETs of the extrahepatic bile ducts is
    a. Growing lump
    b. Changes in bowel or bladder habits
    c. Obstructive jaundice
    d. Persistent pain

Answer Key: c

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