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CASE REPORT | LIVER

Primary Hepatic Neuroendocrine Carcinoma: A Rare Entity

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ABSTRACT

Neuroendocrine tumors are typically low-malignancy growths arising from neuroectodermal cells of neural crest origin. Neuroendocrine carcinoma, on the other hand, represents a high-malignancy form of these tumors. While rare in the liver, they often indicate metastasis when present. We present a unique case of incidentally discovered primary hepatic neuroendocrine carcinoma. Initially, the patient's management was based on misleading radiological findings. However, histopathology confirmed the diagnosis, with subsequent imaging ruling out an extrahepatic source. Despite this, the patient opted against surgical intervention, resulting in a fatal outcome. This case underscores the critical importance of prompt diagnosis and intervention to avert adverse outcomes.

KEYWORDS: neuroendocrine tumor; neuroendocrine carcinoma; hepatic tumor; neural crest

INTRODUCTION

Neuroendocrine tumors (NETs) develop from neuroectodermal cells and usually occur in the gastrointestinal (GI) tract.[1] Liver involvement, although uncommon, is often due to metastasis.[2] We present a unique case of incidentally discovered primary hepatic neuroendocrine carcinoma (NEC), a high-grade malignant NET.

CASE REPORT

A 65-year-old man with type 2 diabetes presented to the emergency department with abdominal pain. For the past week, he experienced right upper quadrant pain, weakness, dark urine, and jaundice. He denied travel, sick contacts, weight loss, or night sweats. He had no history of tobacco, drug, or alcohol use. His family history included stomach cancer in his mother.

His vital signs showed a blood pressure of 81/58 mm Hg and heart rate 107 beats per min. Laboratory results revealed white blood cell count 24.5 000/μL, bilirubin 17.7 mg/dL, aspartate transferase 76 U/L, alanine transferase 128 U/L, and alkaline phosphatase 346 U/L. An abdominal ultrasound revealed a heterogeneous area measuring 9.6 × 9.5 × 7.4 cm in the liver (Figure 1). He had no prior imaging for comparison. Subsequent computed tomography (CT) scan showed a small fluid collection measuring 12.2 × 11.6 × 8.9 cm, concerning for a hepatic abscess or gallbladder carcinoma (Figure 2). The patient was started on intravenous antibiotics with piperacillin and tazobactam; however, after 3 days of no improvement, further workup was pursued. Tumor markers of carcinoembryonic antigen, carbohydrate antigen 19-9, and α-fetoprotein were normal. A percutaneous liver biopsy was performed 1 day later for tissue diagnosis, confirming high-grade small cell NEC, positive for chromogranin, synaptophysin, and insulinoma-associated protein 1 (Figure 3).

Owing to elevated bilirubin and concern for bile duct involvement, a magnetic resonance cholangiopancreatography was performed 3 days later, which revealed a 12.2 × 11.1 cm liver mass obstructing the common bile duct, causing biliary ductal dilation (Figure 4). The patient underwent endoscopic retrograde cholangiopancreatography the next day for biliary decompression, where a proximal

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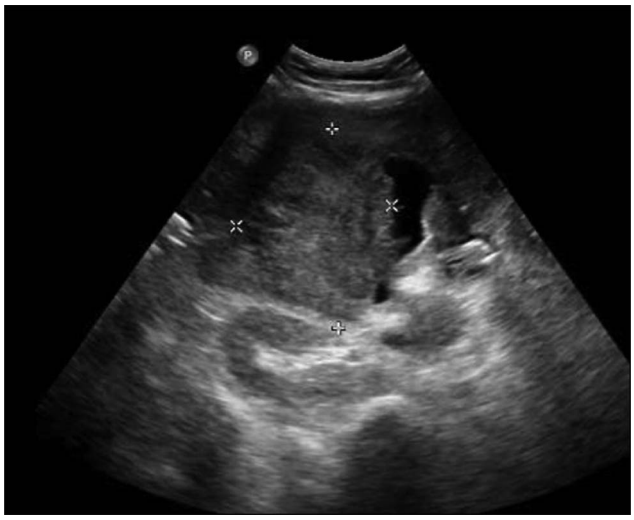

Figure 1. Abdominal ultrasound showed a heterogeneous area measuring 9.6 × 9.5 × 7.4 cm in the mid to lower liver.

biliary stricture was identified and a plastic stent was inserted. Cytology brushing confirmed atypical small cell groups consistent with NEC. Five days later, further staging CT scans of the chest, abdomen, and pelvis, along with a positron emission tomography scan, excluded an extrahepatic origin of the tumor (Figure 5). Despite recommendations for surgery, the patient chose conservative therapy and started carboplatin chemotherapy and was discharged after 12 days. Etoposide was added by the oncology department outpatient. However, unfortunately, his cancer progressed and he died 6 months later.

DISCUSSION

NETs commonly arise in the GI tract (48%), lung (25%), and pancreas (9%), with potential to develop elsewhere.[3] They originate from the foregut (lungs, thymus, esophagus, pancreas, stomach, duodenum), midgut (small intestine, appendix, right colon), and hindgut (transverse colon, descending colon, sigmoid colon, rectum).[3] They can be subclassified based on the mitotic and Ki-67 indices into low malignancy (grade 1), moderate malignancy (grade 2), and high malignancy (grade 3).[4] A lower proliferation index is associated with better survival rates.[2] Grade 3 NETs are classified as NEC, characterized by poorly differentiated cells.[2,4] For the purpose of this case report, the discussion will focus on NETs as NECs are a rare subtype, differentiated only through histopathology, with limited dedicated literature available.

While NETs are common in the GI system, they are rare in the liver, often resulting from metastasis.[5] Primary hepatic NETs account for approximately 0.3% of primary NETs.[6] They were first described in 1958 by Edmondson et al, and around 150 cases have been reported.[2] The origin is debated, with theories including ectopic pancreatic or adrenal cells, neuroendocrine tissue in the intrahepatic biliary epithelium, or chronic inflammation in the biliary tract causing metaplasia.[6]

Primary hepatic NETs typically occur in patients aged 40–50 years, with no specific gender predominance, and no risk factors have been identified.[6] They can be functional, causing skin flushing, diarrhea, and abdominal pain due to hormone secretion (carcinoid syndrome), or be non-functional.[5,7] They grow slowly without symptoms and are often discovered incidentally at advanced stages.[5,7] Symptoms may include weight loss, fatigue, abdominal distension, pain, and a mass in the right upper quadrant.[2]

NETs are challenging to diagnose due to the lack of distinctive features.[4] They can resemble other liver lesions, such as hepatocellular carcinoma (HCC), cholangiocarcinoma, or metastatic carcinoma.[6] Ultrasound may show multiple cystic lesions or a solid mass.[8] Contrast-enhanced CT scans often show primary

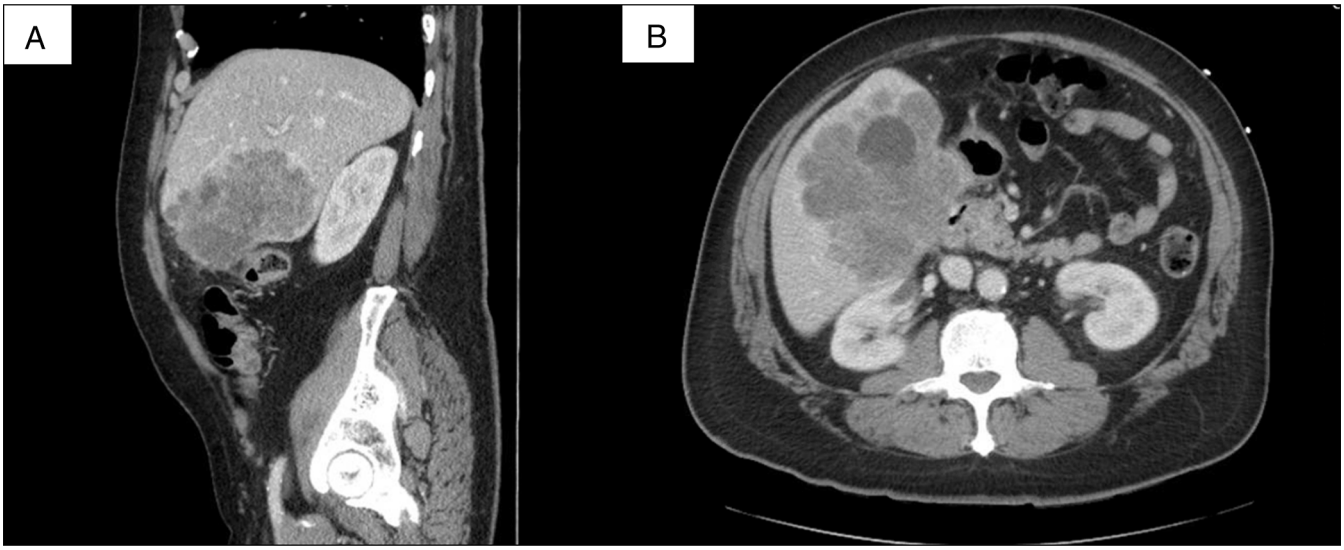

Figure 2. (A and B) Computed tomography scan of the abdomen and pelvis revealed a 12.2 × 11.6 × 8.9 cm small fluid collection with heterogeneous enhancement in the inferior aspect of the liver.

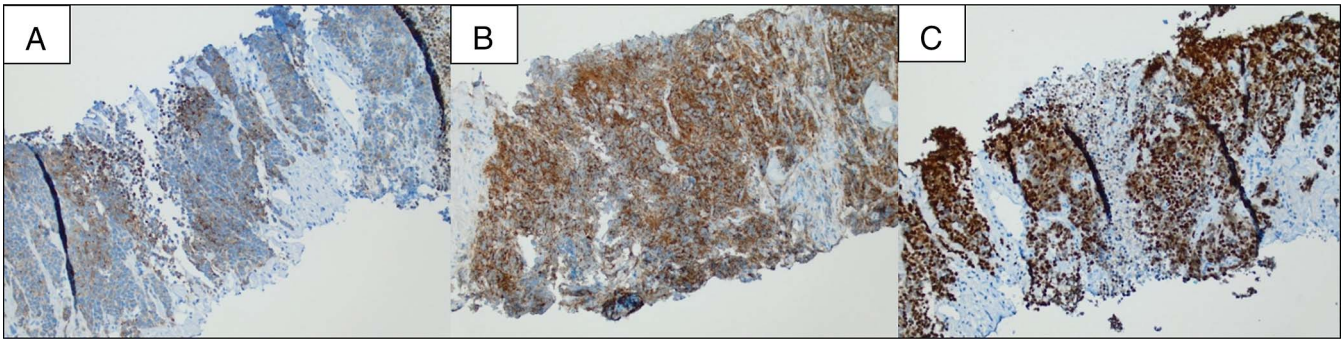

Figure 3. (A, B, and C) Liver histopathology showed positive staining for chromogranin (A, 20×), synaptophysin (B, 20×), and insulinoma-associated protein 1 (C, 20×), all consistent with a high-grade small cell neuroendocrine carcinoma.

NETs as cystic lesions with arterial phase contrast and portal phase washout due to hypervascularity, similar to HCC.[8,9] On magnetic resonance imaging, they typically appear hypointense on T1-weighted images and hyperintense on T2-weighted images.[9] Distinguishing primary from extrahepatic NETs relies on radiographic studies, as histology alone is insufficient.[8] Positron emission tomography scans using ^{11}C-5 hydroxytryptophan tracer have successfully identified the primary tumor in 84% of cases but are limited to a few medical centers.[8] Octreotide scintigraphy is another effective option, with a specificity of 83%.[8] Serum tumor markers are not helpful and are usually negative.[2,7]

Histopathological evaluation is crucial for diagnosing NETs, although the accuracy of preoperative fine-needle biopsy has been inconsistent.[7] In reviewed cases, needle biopsy confirmed with surgical resection was accurate in only 11.3% (14/124 cases), leading to a misdiagnosis of HCC or cholangiocarcinoma.[8] Pathological examination after resection is more accurate, likely because of the larger sample size.[2,7] Biopsies are typically stained with hematoxylin and eosin dye for tumor classification.[7] Histopathology reveals solid and cystic components, with or without necrosis or bleeding.[4] Microscopically, tumors exhibit nested, trabecular, or microacinar architecture with small, uniform tumor cells containing granular chromatin, round nuclei, and stromal hyalinization.[4] Immunohistochemistry is considered the most accurate method to reveal specific markers such as chromogranin A, synaptophysin, neuron-specific enolase, and CD56.[4,7]

Treatment of primary hepatic NETs can be surgical and/or medical.[7] Surgical intervention has shown superior efficacy with a 74% 5-year survival rate and an 18% recurrence rate, depending on the tumor's size and location.[7,9] Alternative modalities such as selective hepatic artery embolization, radiofrequency ablation, or hepatectomy with liver transplantation may be necessary for tumors involving both liver lobes.[7] Medical options for unsuitable surgical transarterial chemoembolization candidates include transarterial chemoembolization, chemotherapy, local ablation, or somatostatin analogs.[4,7] Transarterial chemoembolization has shown promising short-term responses. The effectiveness of chemotherapy, particularly combination treatments such as 5-fluorouracil, doxorubicin, and streptozocin, has not been well studied, although it has been used in nonsurgical patients.[4,7]

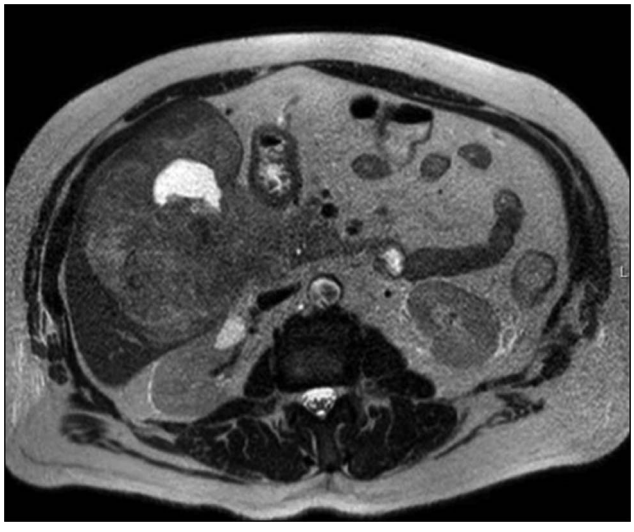

Figure 4. Abdominal magnetic resonance cholangiopancreatography demonstrated a 12.2 × 11.1 cm liver mass with metastasis to the portacaval lymph node, potentially causing direct invasion and partial obstruction of the common bile duct.

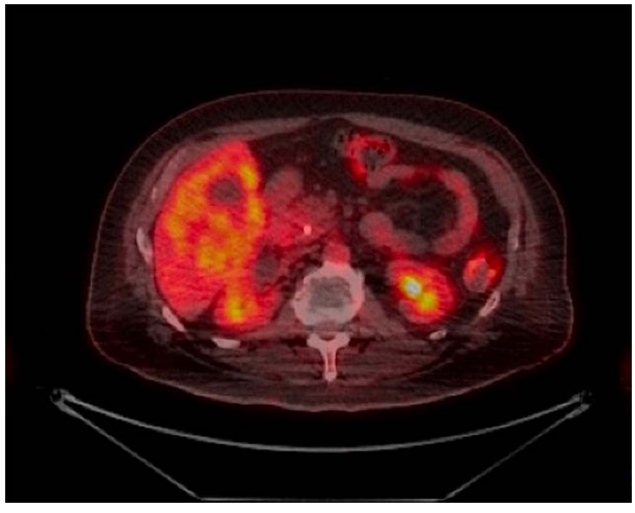

Figure 5. Positron emission tomography scan revealed increased fludeoxyglucose F18 uptake in a large hepatic mass and a portacaval nodal mass, with no other areas of hypermetabolic pathology observed.

In conclusion, primary hepatic NETs require histopathology for a definitive diagnosis due to overlapping radiographic features with other liver neoplasms. NECs are high-grade NETs with poorly differentiated cells. Radiological studies aid in distinguishing primary from extrahepatic NETs. While surgical intervention is preferred, research is needed on chemotherapy's role as a conservative option. Prompt diagnosis and intervention are crucial to prevent adverse outcomes. Future directions could include dedicated research on hepatic NECs.

DISCLOSURES

Author contributions: J. Tidwell designed and drafted the work; B. Thakkar drafted the work; M. Nguyễn critically reviewed the work; S. Parker provided histopathology figures and descriptions; A. Schoenfeld critically reviewed the work and approved for publication. J. Tidwell is the article guarantor.

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