A Diagnostic Dilemma: Metastatic Neuroendocrine Tumor Mimicking Hepatocellular Carcinoma

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ABSTRACT

Carcinoid syndrome arises from neuroendocrine tumors, characterized by the presence of neurosecretory granules. The diagnosis of carcinoid syndrome involves biochemical testing and various imaging techniques. We report the case of a 62-year-old man with Parkinson's Disease who was found to have new-onset cirrhosis and multiple hepatic lesions with necrosis on CT imaging. These findings were concerning for metastatic malignancy of unknown primary origin. Subsequent MRI characterization of the liver lesions indicated hepatocellular carcinoma as the most likely diagnosis. However, a transthoracic echocardiogram, performed for anasarca and dyspnea on exertion, revealed a thickened tricuspid leaflet, highly suspicious for carcinoid valvulitis. A biopsy of one of the hepatic lesions was consistent with neuroendocrine tumor, confirming the diagnosis of carcinoid syndrome. This case highlights the limitations of diagnostic imaging approaches in distinguishing hepatocellular carcinoma from neuroendocrine tumors.

KEYWORDS: neuroendocrine tumor, hepatocellular carcinoma, carcinoid syndrome, carcinoid valvulitis

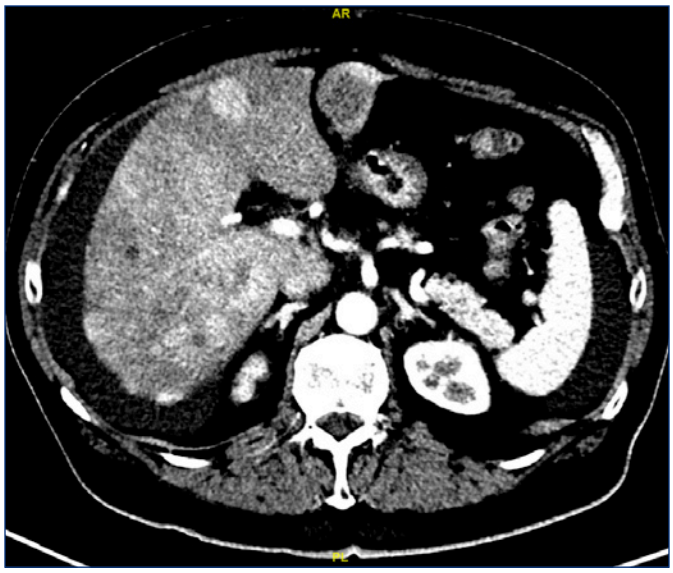
BACKGROUND

Neuroendocrine tumors (NETs) are malignancies originating from the neuroendocrine system and are characterized by the presence of neurosecretory granules.[1] These tumors typically arise from the gastrointestinal tract, pancreas, or lungs and are classified by their grade of differentiation and malignancy.[2] Well-differentiated NETs exhibit low proliferation, while poorly differentiated ones have high proliferation rates.[3] The liver serves as the most common site for NET metastases and can mimic hepatocellular carcinoma (HCC) on presentation.[4]

CASE REPORT

A 62-year-old man with a history of Parkinson's disease, autism and schizophrenia was admitted to the hospital due to new findings on a CT scan that was ordered by his primary care provider [**Figure 1**]. The patient presented to his primary care physician with complaints of poor appetite and an unintentional 40-pound weight loss over the course of one year. He reported four months of exertional dyspnea, fatigue, generalized abdominal discomfort, intermittent diarrhea, nausea, and vomiting. The patient did not drink alcohol, and his colonoscopy two years prior was remarkable for a single tubular adenoma that was removed. Family history revealed siblings with rectal, breast, and prostate cancer.

Figure 1. Initial CT from outside facility, liver window demonstrating numerous hepatic lesions with stigmata of necrosis.



His initial physical exam noted significant pitting edema tracking from his lower extremities and up to his lower abdomen. His labs on admission were notable for acute kidney injury (AKI). His tumor markers, infectious disease laboratory results and antitrypsin levels are noted in **Table 1**. The CT scan of chest, abdomen, and pelvis demonstrated bilateral pulmonary nodules, obstructing right hydroureteronephrosis, cirrhosis, and numerous hepatic lesions with stigmata of necrosis.

The patient was started on diuretics for ascites and peripheral edema. A diagnostic and therapeutic paracentesis yielded 1.3 L of ascitic fluid with a serum ascites albumin gradient (SAAG) consistent with portal hypertension. His AKI worsened with his trial of diuresis.

A transthoracic echocardiogram (TTE) was performed and revealed severe tricuspid, mitral, and pulmonic insufficiency

Table 1. Inpatient Liver function test, cancer workup, and ascites workup values. (Abnormal values are bolded.)

AST (10–42 IU/L)	40	**117**	**508**
ALT (6–45 IU/L)	25	**16**	**60**
Alkaline Phosphatase (34–104 IU/L)	**154**	**111**	**107**
Total Protein (6–8 G/L)	7.3	**5.8**	**5.6**
Albumin (3.5–5 G/dL)	4.1	**3.4**	**3.4**
Total bilirubin (0.2–1.3 Mg/dL)	2.1	2.2	3.4
Direct bilirubin (0–0.3 Mg/dL)	0.8	—	—
Alpha 1 antitrypsin antinuelcar antibody (90–200 MG/DL)	233		
Alpha fetoprotein (AFP) (0.0–10 ng/mL)	3.6	—	—
Carbohydrate antigen 19–9 (CA 19–9) (0.0–35.0 U/ML)	4.5	—	—
Beta human chorionic gonadotropin (0.0–5.0 MIU/ML)	< 2.0	—	—
Lactate dehydrogenase (10 –200 IU/L)	172	—	—
Serum ascites albumin gradient (SAAG) (g/dL)	1.8	—	—

Table 2. Abbreviated basic metabolic panel and brain natriuretic peptide (Abnormal values are bolded.)

Labs (Reference Range)	Inital values	Day 8 values	Day 9 values
Sodium (135–145 mEQ/L)	**133**	**134**	135
BUN (6–24 Mg/dL)	**31**	**58**	**70**
Serum Creatinine (0.64–1.27 Mg/dL)	**1.85**	**3.07**	**3.78**
Brain natriuretic peptide (BNP)	820	—	—

as well as thickened tricuspid leaflets [**Figure 2**]. This was highly suspicious for carcinoid valvulitis. The patient's metastatic lesions were evaluated with further imaging. An MRI of the abdomen demonstrated washout consistent with hepatocellular carcinoma (HCC), as demonstrated in [**Figure 3**].

Based on the available data, the differential diagnosis included stage 4 HCC with Child Pugh Class B cirrhosis and carcinoid syndrome with resultant carcinoid valvulitis. The consulting oncology and cardiology teams recommended a liver biopsy and 24-hour urine 5-Hydroxyindoleacetic acid (5-HIAA) collection. A peripheral liver lesion was biopsied, and the urine collection was deferred due to biochemical interference from the patient's home carbidopa-levodopa.[5] On hospital day 8, the patient's laboratory values were remarkable for worsening AKI, and the patient became progressively encephalopathic and oliguric. The patient expired the following day.

The final liver biopsy report was released after the patient's death, and demonstrated, tumor cells positive for chromogranin and synaptophysin, supporting a neuroendocrine tumor diagnosis. The tumor cells were positive for CDX2, suggesting a primary gastrointestinal neoplasm. [**Figure 4**]

Figure 2. TTE valvular view demonstrating aortic regurgitation.

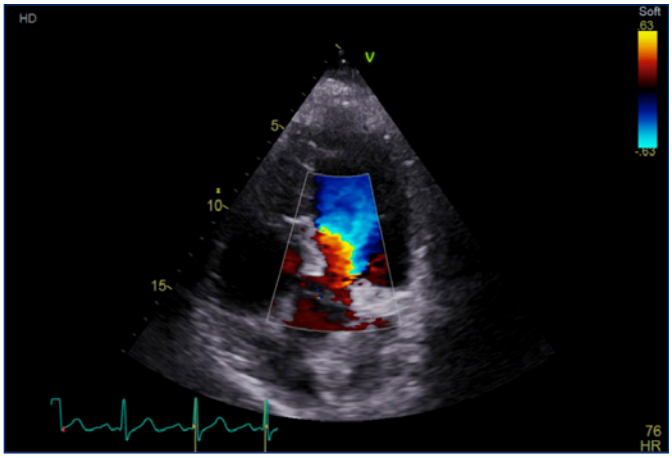


Figure 3. The image demonstrates multiple arterially enhancing lesions within the liver. The largest is a 3.8 x 4.6 cm enhancing lesion.

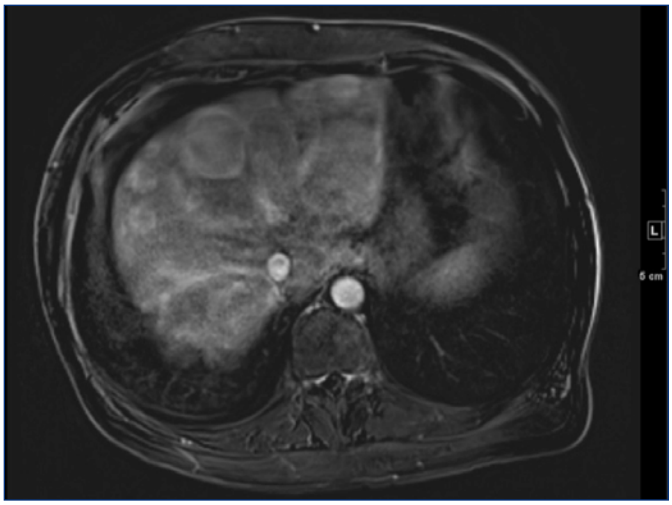
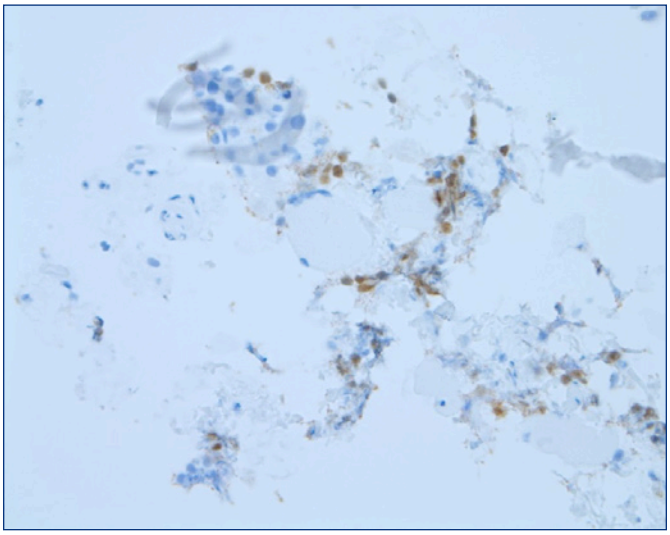


Figure 4. Histology slides of liver biopsy with CDX2 stain. Brown cells are positive for CDX2.



DISCUSSION/CONCLUSION

This report presents a rare case of NETs mimicking HCC. The classic presenting symptoms of HCC include right upper quadrant pain, weight loss, jaundice, and ascites.[6] The MRI findings strongly suggested a diagnosis of metastatic HCC. However, it was significant that the patient lacked the risk factors for HCC such as viral hepatitis infection, chronic alcohol consumption, and comorbidities of non-alcoholic fatty liver disease.[7] Furthermore, alpha fetoprotein was within normal limits.[8]

The characteristic TTE findings of carcinoid syndrome argued against a diagnosis of HCC. The natural history of carcinoid syndrome typically involves several years of vague abdominal pain, with characteristic systemic symptoms developing following metastasis to the liver. The classic symptoms of carcinoid syndrome subsequently develop flushing (84% of patients), diarrhea (70%), heart disease (37%), and bronchospasm (17%).[9] Carcinoid valvulitis results from the oversecretion of vasoactive amines, such as serotonin, leading to the fibrous, plaque-like deposits on the right side of the heart. Over time, the tricuspid leaflets become fixed, leading to stenosis and regurgitation.[10]

Imaging plays a central role in the diagnosis of HCC. For diagnostic testing, multiphasic, contrast-enhanced, multidetector row CT or MRI is recommended. Arterial enhancement is required for hepatic lesions to be considered suspicious for HCC, and washout on portal or delayed phases are additional features of HCC. Washout refers to hypodense or hypointense appearance of lesions compared to liver parenchyma. According to the American Association for the Study of Liver Diseases (AASLD) guidelines, a single modality CT or MRI is sufficient when hallmark features are present in nodules >1 cm.[11] Based on these guidelines, radiologists might favor a diagnosis of HCC. However, metastatic hepatic NETs have similar imaging findings. The unique imaging feature that helps differentiate metastatic hepatic NETs is Gallium-68 DOTATATE uptake on nuclear imaging, which takes advantage of somatostatin receptors in NETs.[12] Some studies have documented somatostatin receptors in more than one-third of HCCs, and a case report has noted HCC mimicking NETs on Gallium-68 DOTATATE imaging.[13] This highlights the need for specific imaging biomarkers that employ tumor biology to aid in the differentiation of NET from HCC. A radiotracer currently under investigation using this approach is [68Ga] Ga-NOTA-MAL-Cys39-exendin-4. This tracer involves labeling the peptide Exendin-4 with Gallium-68. Exendin-4 acts as an agonist for the Glucagon-like peptide-1 receptor (GLP-1R), which is expressed in insulinomas, a common type of functional pancreatic NET. [68Ga] Ga-NOTA-MAL-Cys39-exendin-4 demonstrates high accuracy in localizing insulinomas, eliminating the need for somatostatin receptor binding, which is typically absent in insulinomas.[14]

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