

# Solitary hypervascular liver metastasis from neuroendocrine tumor mimicking hepatocellular cancer: All that glitters is not gold

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## ABSTRACT

Neuroendocrine tumor metastases to the liver can mimic primary hepatocellular carcinoma (HCC) on imaging, cytology, and core biopsy. We present a case study along with the literature review of a patient who presented as a solitary liver mass mimicking HCC and subsequently underwent a partial hepatectomy. The histopathology and immunohistochemistry of the resected specimen revealed metastatic neuroendocrine carcinoma. Positron emission tomography (PET) scan with <sup>68</sup>Ga-DOTA-Nal-octreotide (<sup>68</sup>Ga-DOTANOC) localized the primary tumor in the ileum. A curative follow-up surgery for resection of the small bowel containing the primary tumor was carried out. This case illustrates the shortcomings of routine imaging methods, utility of immunocytochemistry and the importance of <sup>68</sup>Ga-DOTANOC PET in determining the metastatic spread as well as the origin of neuroendocrine tumors (NETs). This case report attempts to highlight the current imaging paradigms and management strategy of midgut and other NET's at the point of detection, staging and follow-up.

**Keywords:** Computed tomography, DOTA-Nal-octreotide positron emission tomography, hepatocellular carcinoma, immunohistochemistry, magnetic resonance imaging, neuroendocrine tumor

## INTRODUCTION

The diagnosed incidence of neuroendocrine tumors (NETs) in the current decade has risen to 5/100,000 from about 1 to 2 cases per 100,000, three decades ago.<sup>[1]</sup> This can be attributed to advanced diagnostic radiological and pathological techniques available in medical science today. Multi detector computed tomography (CT) techniques with dynamic scanning of the abdomen in the arterial phase to detect hypervascular lesions such as those found in NET is routine protocol for patients who have a clinical suspicion of the tumor. Similarly, functional imaging such as nuclear positron emission tomography (PET) scans with <sup>68</sup>Ga-DOTA-Nal-octreotide (<sup>68</sup>Ga-DOTANOC) has further narrowed the possibility of detecting these lesions. Immunohistochemistry is an integral part of the diagnostic

confirmation algorithm. We present a perplexing case of a patient who presented with a solitary liver mass, mimicking hepatocellular carcinoma (HCC), on imaging and cytopathology and was subsequently operated for the same. A fluorodeoxyglucose (FDG) PET scan done before the surgery did not detect the primary tumor. The patient was diagnosed to have a metastatic secondary in the liver from a primary NET, only after histopathology and immunohistochemistry of the explanted liver was performed. Further evaluation in the postoperative period with <sup>68</sup>Ga-DOTANOC PET enabled the localization of the primary tumor in the midgut, which was then re-explored and excised with a follow-up surgery. This case highlights the importance of immunohistochemistry for suspected hypervascular mass lesions in the abdomen. In addition, it emphasizes the relevance of functional imaging with <sup>68</sup>Ga-DOTANOC PET and pitfalls of FDG PET in the assessment of hypervascular tumors of the abdomen and gastrointestinal tract. The use of <sup>68</sup>Ga DOTANOC PET in the first stage of evaluation of the liver mass, along with FDG PET could have pointed to the nature of the mass and thus saved the patient morbidity related to two consecutive major laparotomy procedures. On review of the literature, we came across only one case report, which showed a primary HCC metastasis to pancreas resembling a NET, however no other such mimic cases have been reported.

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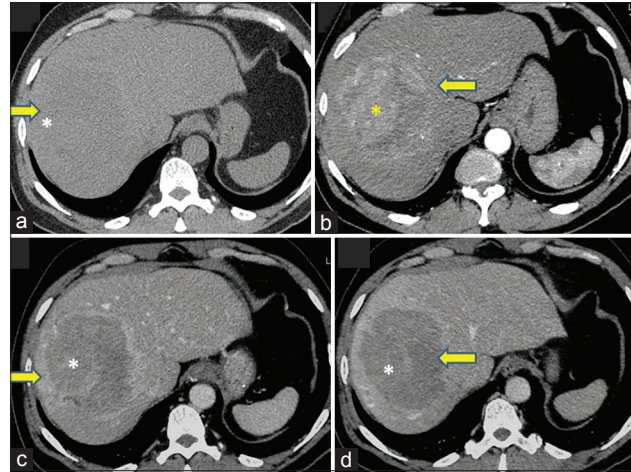
## CASE REPORT

A 55-year-old male presented to our hospital with continuous vague pain in the upper abdomen for a month. No other positive history of chronic diseases, prodromal symptoms, altered bowel habits, weight loss or gastrointestinal bleed was elicited. Ultrasound abdomen, performed at an outside hospital had revealed a space-occupying lesion in the liver for which he underwent a fine-needle aspiration and cytology (FNAC). The available report of the above (done elsewhere) showed HCC; however no slides were made available for review. Physical examination did not show any positive findings, and the patient underwent a contrast-enhanced computed tomography (CECT) of the upper abdomen for further evaluation and staging of the mass lesion in the liver. The CECT revealed underlying diffuse hepatomegaly with hepatosteatorosis. An arterial phase enhancing, well defined lobulated, rounded, hypervascular lesion measuring approximately 10 cm in its largest diameter was present in the right lobe of the liver (segments VIII and V) [Figure 1a-d].

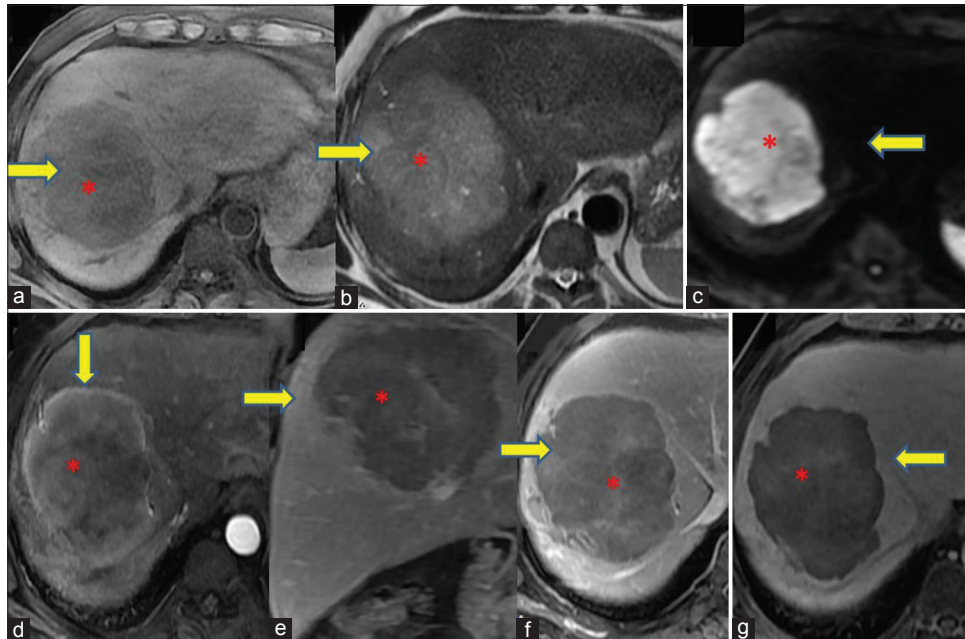
In addition, a contrast-enhanced magnetic resonance imaging (CEMRI) with hepatocyte-specific contrast (Gadolinium – BOPTA, Bracco) was performed for further characterization of the mass and to look for satellite lesions that may have been missed on CT. The CEMRI showed T1-weighted hypointense, T2-weighted hyperintense and diffusion restriction of the mass. With subsequent washout on portal venous and delayed hepatobiliary phase obtained at 90 min

post injection [Figure 2a-g]. It showed hypervascularity of the lesion on arterial phase.

This suggested predominance of non hepatocyte cellular contents within the mass. Differential diagnosis of primary hepatocellular cancer and solitary hypervascular metastasis from an occult primary was made. In view of the above findings and



**Figure 1:** A 55-year-old gentleman with solitary hypervascular mass in the right lobe of liver on dynamic computed tomography (CT). (a) Mildly hypodense mass (\*) in the region of right lobe of liver on noncontrast CT scan. (b) The mass (\*) shows arterial hypervascularity along its periphery (bold arrow). (c) The lesion showed contrast washout on the portal venous phase and was seen to encase the anterior division of the right portal vein. (d) Washout persistent in the equilibrium phase in the mass (\*)



**Figure 2:** A 55-year-old man with hypervascular hepatic neuroendocrine tumor secondary deposit. (a) The fat-suppressed T1-weighted fast spin-echo, magnetic resonance imaging (MRI) image performed after the dynamic computed tomography (CT) shows a hypointense mass (\*) in right lobe (block arrow) (b) The fat-suppressed T2-weighted fast spin-echo, MRI image performed after the dynamic CT shows a hyperintense mass (\*) in the right lobe of liver (block arrow) and in caudate lobe (open white arrow). (c) The axial diffusion weighted image of b value 1000 shows restriction of the lesion (\*) on T2-weighted (block and open arrows). b value = 1000. (d) The fat-suppressed T1-weighted fast spin-echo, dynamic MRI in the arterial phase shows a hypervascular enhancing mass (\*) in the right lobe of liver (block arrow) (e) Fat-suppressed T1-weighted fast spin-echo, dynamic MRI in the portal venous phase shows an encapsulated mass (\*) with central washout in the right lobe of liver (block arrow). (f) The fat-suppressed T1-weighted fast spin-echo, dynamic magnetic resonance imaging MRI in the equilibrium phase shows an encapsulated mass (\*) with better visualized central hypointensity in the right lobe of liver (block arrow). (g) The fat-suppressed T1-weighted fast spin-echo, dynamic MRI in the hepatocyte specific phase at 90 min shows an encapsulated mass (\*) with central hypointensity in the right lobe of liver (block arrow)

previously conducted FNAC, the diagnosis of HCC was primarily considered, and an FDG PET scan was conducted to rule out occult primary or distant secondaries before subjecting the patient to hepatectomy. No obvious evidence of FDG PET avid lesion or extrahepatic disease was found on the PET scan. With a provisional diagnosis of primary HCC without extrahepatic spread, the patient underwent a modified right extended hepatectomy to excise the mass. No obvious extrahepatic disease was identified during the course of the laparotomy. Right hepatectomy specimen was sent for histopathological analysis [Figure 3a and b] on gross pathology examination; transection margin was found to be 1 cm away from the tumor mass and was free from the tumor [Figure 3c].

The uninvolved liver parenchyma was non cirrhotic. On microscopic examination of the sections from the tumor, lobular architecture comprising of thickened trabeculae nests, insular pattern and acini separated by fine endothelial network with a mild amount of interspersed fibrous stroma was found. On immune histochemical analysis, tumor cells showed strong immunostaining with synaptophysin and chromogranin-A with Ki-67 immunolabelling index of < 2%. A diagnosis of metastatic neuroendocrine carcinoma, with small and large vessels invasion, was made. In view of the metastatic neuroendocrine nature of the liver lesion, a DOTANOC PET scan was done to look for the primary, as well as any other occult secondary deposits in the abdomen. The scan was suggestive of nodular activity in the distal small bowel mesentery, in the right lower abdomen with an associated reactive focus in the ileum [Figure 4a-c].

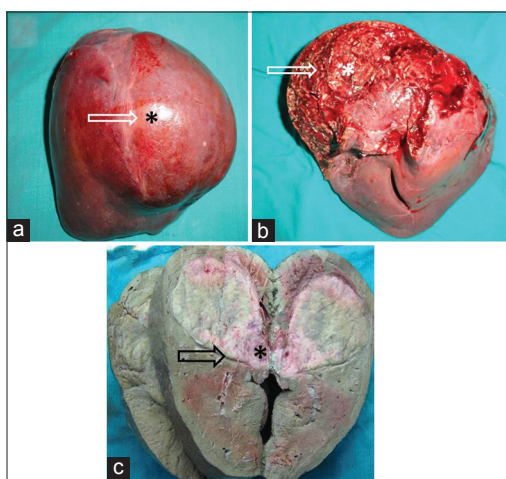
Subsequently the patient was posted for a follow-up surgery at 4 weeks from the previous hepatectomy. The repeat laparotomy revealed a stricture in the long segment of the distal ileum with multiple small nodules and ulceroproliferative lesions in the mucosa for a span of approximately 30 cm. An additional small mass lesion in the terminal ileum with mesenteric invasion and desmoplastic reaction was localized which was subjected to

en block resection with end to end anastomosis of the ileum. Tumor histopathology showed serosal invasion and loco regional metastases to the ileal lymph nodes. On immunohistochemistry, the tumor was synaptophysin, chromogranin-A positive with Ki-67 index < 2% with the final diagnosis of multicentric neuroendocrine carcinoma (pathological staging of IV). The patient had an uneventful postoperative period and was free at a year's follow-up.

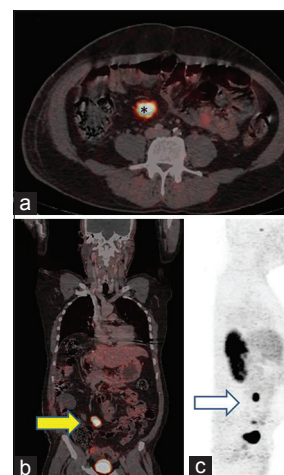
## DISCUSSION

### Pathophysiology and incidence

The term “neuroendocrine” in NETs derives from precursor cells of these mass lesions, which are essentially endocrine cells with nerve cell antigens. These cells normally evolve into endocrine glands which are an essential element of the neuroendocrine system and are classically found in the small bowel, where they are involved in gut motility as well as secretion of metabolically active substances such as serotonin, chromogranin, kinins, prostaglandins and various other growth factors.<sup>[2-5]</sup> NETs are most commonly seen in the midgut (ileum and jejunum), pancreas as well as large bowel.<sup>[6]</sup> They can also originate in other parts of the body. Secondaries from gastroenteropancreatic NETs are most commonly found in the liver. NETs are known to have an incidence of 1-3/100,000.<sup>[7]</sup> Many of these tumors are incidentally detected during the course of investigations or at the time of autopsy.<sup>[8,9]</sup> As the name suggests, NETs are comprised of endocrine cells that may or may not secrete hormones and hence are classified as functional or nonfunctional tumors.<sup>[10]</sup> The nonfunctioning NETs are usually asymptomatic and difficult to diagnose based on the clinical history.<sup>[11]</sup> For example, in the case discussed above, the patient did not report any endocrine or hormonal imbalances, hence the primary was not suspected. Functional tumors manifest with clinical symptoms pertinent to the hormone secreted by the tumor for example serotonin, insulin, glucagon, etc., which are likely to cause endocrinological



**Figure 3:** Explanted right hepatectomy specimen with tumor. (a) Explanted right hepatectomy specimen with tumor (\*). (b) Cut surface of the tumor (\*) specimen after resection. (c) Gross pathology specimen with tumor (\*)



**Figure 4:** (a) Axial section of DOTA-Nal-octreotide (DOTANOC) positron emission tomography/computed tomography (PET/CT) showing reactive focus in the small bowel mesentery (\*). (b, c) Coronal section of DOTANOC PET/CT (bold arrow) and isotope scan (outlined arrow) showing reactive focus in the small bowel mesentery

imbalance. The World Health Organization (WHO) recently introduced a novel classification system for NETs on the basis of tumor grading in 2010. This system utilizes histopathological markers of Ki-67 index, mitotic count, and tumor necrosis and is now being used as standard criteria for histopathological diagnosis and staging of these tumors.<sup>[12]</sup> NETs are associated with syndromes like Von-Hippel-Lindau, multiple endocrine neoplasia type 1 and neurofibromatosis-type 1.<sup>[10,11]</sup> Midgut NETs are second most common malignancy after adenocarcinoma's in the small bowel and are notorious for being asymptomatic or presenting as nonspecific symptoms.<sup>[12]</sup> Midgut tumors form one-fourth of the bulk of diagnosed NETs.<sup>[12]</sup> They have a relatively good prognosis and a 5 year survival rate of > 50% even with synchronous metastatic disease. The hepatic involvement by NETs is seen as: Metastatic spread (in 25–90%), mixed HCC/Adeno-neuroendocrine carcinoma and the primary NET of liver (<0.5% of all NETs) in the same order.

## Diagnosis

There is an increase by 5 times in the detection rate of NETs in the last two decades, partly due to improved radiological techniques.<sup>[2]</sup> The latest epidemiological survey from a south Asian country like Japan shows that almost 20% of patients have distant spread of the disease at presentation. Carcinoid syndrome which is characterized by flushing, diarrhea, and abdominal pain is observed in approximately 3% of the gut tumors.<sup>[8]</sup> Abdominal CT with contrast is the most readily available and simplest method of the preliminary investigation of suspected midgut NETs or tumors.<sup>[7]</sup> CT enterography using positive or neutral oral contrast with adequate small bowel distension and multi-planar reformatting post acquisition facilitates viewing of the small bowel loops.<sup>[9]</sup> The sensitivity of CT and MR Enteroclysis to detect small bowel NETs is 85% and 86% respectively and appears limited, however distant spread and extra-tumoral involvement is well-demonstrated by the above.<sup>[7-9]</sup> At our center, we use the CT enterography technique where oral neutral contrast along with methylcellulose is given to distend the small bowel without any discomfort of inserting the Enteroclysis tube. In cases where the primary site of the tumor is unidentifiable, such as seen in our patient, whole-body scintigraphy using somatostatin receptor scintigraphy (SSRS) for PET/CT (using Gallium-labeled somatostatin analogs) or single-photon emission CT is recommended. It has been established that receptor subtypes, SSTRs 2 and 5 are useful for diagnostic workup of primary NETs.<sup>[2]</sup> <sup>68</sup>Ga-labeled somatostatin analogs are available for PET imaging. DOTANOC binds to SSTR2, SSTR3, and SSTR5 receptors whereas DOTA octreotide (DOTATOC) and DOTA octreotate bind to SSTR2 and SSTR5. These analogues accumulate in the tumor nodules within 100–120 min and can be rapidly imaged.<sup>[10]</sup> The demonstration of somatostatin receptor status by <sup>111</sup>In-octreotide or <sup>68</sup>Ga-labelled peptide PET/CT imaging not only serves as a diagnostic tool but also helps in predicting the response to somatostatin analogue therapy.<sup>[10]</sup> <sup>68</sup>Ga-DOTATOC has higher sensitivity (96%) and specificity (92%) to CT or SSRS for occult primary work up, staging and follow-up of the disease process.<sup>[10]</sup> DOTATOC

is superior in diagnosis of systemic and bony spread however has been found inadequate for detection of liver and lung secondaries where CT is recommended. The unavailability of nuclear scanning on a daily widespread basis and its practical cost implications are the major disadvantage of this technique. It also has its limitations in detection of low receptor density and small (<1 cm) lesions. Recent advances in use of newer agents like <sup>18</sup>F-DOPA for PET/CT has shown even higher sensitivity in metastatic NETs (almost 100%). Premedication with Carbidopa for reduction of artifacts due to normal physiological activity in the peripancreatic tissues has been recommended.<sup>[10]</sup> <sup>18</sup>F-FDG PET/CT is mostly useful for diagnosis and staging of poorly differentiated NETs which essentially are WHO Grade 3 and 4.<sup>[9]</sup> Poorly differentiated midgut lesions with reduced hormone production, and a high cellular proliferative activity have a higher propensity to take up <sup>18</sup>F-FDG as do most other “usual” cancers. This may be the reason that the tumor in distal small bowel (which was not poorly differentiated) in the case described above, could not be detected on FDG PET on the initial screening. This fact suggests that all tumors that have not been histologically defined should undergo both FDG and a DOTANOC PET so as not to miss occult and well differentiated NETs. Also in cases where the clinical suspicion of an NET is high and FDG PET is unable to diagnose the primary, DOTANOC PET or alternate scintigraphy scans may be considered so as not to miss the primary lesion. Other modalities such as meta-iodobenzyl guanidine scans can be used to investigate patients with metastatic disease who may be potential candidates for treatment with radionuclide therapy.

## Management

Debulking of the small bowel primary tumor and subsequent surgical anastomosis is generally recommended in case of midgut NETs because of future beneficial effect in decreasing small bowel and vascular complications.<sup>[11,12]</sup> A multivariate analysis of the study population in the United Kingdom by Niederle MB *et al.* showed that age at diagnosis, Ki-67 level and surgical removal of the primary tumor were standalone predictors of survival in patients with midgut NET and associated hepatic secondaries.<sup>[9]</sup> This is especially true for the nonfunctioning midgut tumors where somatostatin analogs and systemic chemotherapy has limited or essentially no role to play.<sup>[11]</sup> The chances of lymph nodal spread of the disease is seen in almost 60% of small bowel primary NETs. Associated probability of hepatic secondaries at the time of diagnosis is about 30%.<sup>[7]</sup> As discussed in the guidelines of management of midgut NETs by Cheung *et al.* resection of the primary tumor and associated mesenteric lymph nodes is mandatory to treat small bowel NETs, irrespective of the presence of hepatic secondaries or not.<sup>[7]</sup> In addition, this group recommended, that patients who are found to have small bowel NETs, after laparotomy and histopathology, such as in our patient's case, are candidates for further surgery which is beneficial for future prognosis.<sup>[11]</sup>

## Follow-up and tumor response

The modality for follow-up imaging should ideally be the one which was able to detect and diagnose the lesion pretreatment.

SSRS imaging should be performed for SSTR avid tumors with CT and MRI wherever indicated. CT and MRI are the only means of follow-up when tumor is SSTR negative. Frequency of assessment depends on tumor growth rate, and MRI may be used to prevent excessive radiation exposure.

## CONCLUSION

Neuroendocrine tumors are a unique group of tumors pertaining to their etiology, origin and function. They may or may not be easily detected on routine CT and MRI investigations especially if they are “nonfunctional.” Distant spread to the liver may sometimes be the only manifestation of the tumor and despite the frequency of this presentation; it may be a clinically diagnostic challenge. Multidisciplinary approach, in which nuclear medicine techniques play an important role in the detection, staging, follow-up and response of these tumors, is essential. NET metastases to the liver can mimic primary HCC on imaging, FNAC as well as core biopsy. It is crucial to be aware of this pitfall while evaluating solitary hypervascular liver lesions and to develop a robust strategy with judicious use of <sup>68</sup>Ga-DOTANOC and 18F-FDG PET/CT to reach the correct diagnosis as well as staging which has a major role in treatment management and patient prognosis.

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