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Imaging features of malignant abdominal neuroendocrine tumors with rare presentation

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Abstract

Background—Gastroenteropancreatic neuroendocrine tumors (NETs) are rare entities arising from neuroendocrine cells in the gastroenteric tract and pancreas. The purpose of this article is to present four cases of gastroenteropancreatic NETs that featured a challenging diagnosis.

Case Presentation—We report a case series of four NETs, each with different features. All NETs were suspected based on clinical and biochemical data. The workup of the abnormalities was performed with CT, PET or MRI.

Conclusion—The diagnosis of NETs is challenging and generally based on clinical manifestations, blood biochemical tests, imaging techniques, and pathology

Keywords

Neuroendocrine tumors; MRI; octreoscan; insulinoma; glucagonoma; biliary neuroendocrine tumor

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Conflict of interest

None

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1.1 Background

The gastroenteropancreatic tract is the primary location of neuroendocrine tumors (NETs), followed by the respiratory tract. NETs are slow growing tumors previously considered to be mostly benign; since 2010 the World Health Organization (WHO) has considered all gastroenteropancreatic NETs as malignant because of their potential to metastasize [1].

Gastroenteropancreatic NETs arise from neuroendocrine cells originating in the gastroenteric tract or pancreas. Together with respiratory tract NETs (foregut NETs), they form the common entity referred to as NETs. Gastroenteropancreatic NETs were referred to as “carcinoids” in the past [2]. The term “carcinoid” is still used today to indicate a clinically active tumor secreting serotonin. NETs can be classified clinically and pathologically into functioning and non-functioning, the functioning group being further sub-classified into five subtypes according to the hormone or peptide secreted by the tumor: insulinoma, VIPoma, glucagonoma, somatostatinoma, and gastrinoma [1].

The incidence of gastroenteropancreatic NETs is reported to be increasing worldwide [2], the reasons for which is unclear [3]. The latest reported incidence is about 3 cases for every 100,000 persons per year [2]. The rise in incidence may be accounted for by the growth in sensitivity and specificity of diagnostic screening tests [4, 5]. The chances of a NET becoming metastatic and aggressive are dependent on its subtype and on other pathologic characteristics, such as differentiation, ki67, mitotic rate, presence of necrosis; insulinoma is the least aggressive (only 10% of cases reported to be metastatic at the time of diagnosis) and glucagonoma is the most aggressive (up to 80% of cases reported to be metastatic at the time of diagnosis) [6]. Lymph node metastases are twice as likely to present at the time of diagnosis compared with liver metastases.

Prior to the 2010 WHO classification which considered all gastroenteropancreatic NETs to be malignant, NETs could be considered as either benign or malignant. Thus, two main characteristics have been important in describing the clinical features across the various NETs: their capability to secrete hormones and their propensity to metastasize. The presence of metastases was considered the only biological feature distinguishing between benign and malignant NETs, since no other biochemical, imaging, or genetic features could help on that regard [7].

To appropriately care for patients affected by NETs, accurate detection and characterization of the primary lesion, as well as determination of local extent and presence of metastases are required. For this purpose morphologic imaging such as ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI) are used. Another important step when the diagnosis is unclear with morphologic imaging is the functional evaluation of somatostatin transmembrane receptor (SSTR) density with molecular imaging techniques such as PET/CT with ⁶⁸Gallium-labelled radiotracers, such as ⁶⁸Ga-DOTA-TATE, ⁶⁸Ga-edotreotide and ⁶⁸Ga-DOTA-NOC[8].

In the case of the most frequent subgroup of functional NETs, clinical and laboratory data are useful to suspect the neoplasms; therefore, diagnostic imaging is requested to confirm the clinical suspicion. In the case of rare nonfunctional NETs, the non-specificity of the

clinical features does not help the radiologist to reach an early diagnosis and differentiate against other neoplasms. In these cases, the radiologist should be aware of differential diagnosis among other solid lesions (such as pancreatic adenocarcinoma (PDAC) in case of a pancreatic lesion), or anatomic variants and pseudo-lesions.

We present the imaging features of four cases of malignant NETs of the gastroenteropancreatic tract, each with different rare features. We focus on presenting these imaging features in conjunction with their clinical and diagnostic features, and their treatment as performed in our tertiary cancer center.

2.1 Case Presentation

We report a series of four cases of NETs, metastatic at the time of the diagnosis, with rare or uncommon sites of presentation. Written informed consent for this case report series was not required, as established by our institutional review board policies. The clinical and imaging features of these patients are summarized in Table 1.

2.1.1 Patient demographics and clinical data

Patients ranged in age between 43 and 73 years, with a mean age of 59 years. Three (75%) were men. The four pathology-proven subtypes were: case 1, gastrinoma in a patient found to have multiple endocrine neoplasia type 1 (MEN-1); case 2, glucagonoma; case 3, low grade insulinoma; and case 4, primitive biliary neuroendocrine. Three patients (cases 1–3) were symptomatic at presentation, the symptoms being related to the primitive subtype of the tumor. Laboratory abnormalities were found in all patients: the patient with gastrinoma had mild anemia (hemoglobin 11.5 g/dL, normal range 13–17 g/dL; hematocrit 33.5%, normal range 38–52%) and elevation of serum calcium (12.5 mg/dL, normal range 8.5–10.5 mg/dL); the patient with glucagonoma had increased AST (94 U/L, normal range 10–37), ALT (178 U/L, normal range 5–37), alkaline phosphatase (289 U/L, normal range 45–129), and gamma-glutamyl transferase (491 U/L, normal range 0–45); the patient with low grade insulinoma had hypoglycemia; and the patient with primitive biliary neuroendocrine had elevation of AST (62 U/L, normal range 10–37 U/L), ALT (97, normal range 5–37 U/L), and CA 19-9 (109 U/mL, normal range 0–40 U/mL).

2.2.2 Imaging features

The three symptomatic patients underwent Contrast Enhanced Computed Tomography (CECT) (Figures 1,2,3) and the one asymptomatic patient underwent Magnetic Resonance Imaging (MRI) because of previous allergic reaction to iodinated contrast medium (Figure 4). Specifically, the workup for all cases consisted of: case 1, CECT followed by endoscopic biopsy; case 2, CECT followed by ultrasound-guided biopsy; case 3, CECT followed by ultrasound-guided biopsy and thereafter Single-photon emission computed tomography (SPECT)-CT OctreoScan with ¹¹¹In pentetreotide; and case 4, MRI and ultrasound-guided biopsy.

Two tumors were localized in the pancreas: the tumor in case 3 was localized in the body/tail of the pancreas while the tumor in case 2 was localized in the tail of the pancreas. The tumor was localized in the stomach and duodenum in case 1. The tumor was localized in the right

hepatic duct in case 4. Three tumors exhibited multiple liver metastases; the exception was case 4, in which the patient with asymptomatic primitive biliary neuroendocrine had no visible metastases. All lesions enhanced in the early arterial phase with wash-out of contrast in the delayed phase, either on CECT or MRI. The case 4 patient had dilatation of the right biliary ducts. Enlarged lymph nodes were seen in three out of four cases: case 1, 2 and 3.

2.2.3 Outcomes

All patients underwent biopsy, either ultrasound-guided (3 cases) or endoscopically (1 case). The patient with primitive biliary neuroendocrine underwent hepatectomy, bile duct resection with cholecystectomy, and Roux-en-Y biliary reconstruction, and ten years after surgery had no evidence of recurrence. The patient with multiple gastrinomas in stomach and duodenum was diagnosed with MEN-1.

3.1 Discussion and Conclusion

All four cases were rare or unique in their clinical presentation and diagnosis workflow. We will highlight the most important characteristics of NETs in conjunction with the diagnostic workflows when necessary.

3.1.1 Etiology

Despite arising from many different embryological origins, NETs have common phenotypic characteristics and therefore can be considered as a unique group. The most important and widely accepted characteristic of all NETs is the expression of neuroendocrine tissue markers, proved with immunoreactivity stains such as chromogranin, synaptophysin, and neuron-specific enolase (NSE) [9, 10]. Despite the previously accepted theory that all NETs arise from cells in the neural crest, it seems more likely that all gastroenteropancreatic NETs derive from a pluripotential cell progenitor which expresses some neuroendocrine features due to a somatic mutation [11]. The etiology of NETs is not fully explained. Most NETs are sporadic but there is a small familial risk. NETs are associated with complex hereditary cancer syndromes such as MEN Type 1 and 2 (MEN-1 and MEN-2) [12], neurofibromatosis type 1 (NF1) [13], and Von Hippel Lindau syndrome (VHL) [14].

3.1.2 Diagnostic features

The diagnosis is generally based on clinical manifestations, blood biochemical tests, imaging techniques, and pathology [2].

The universal marker associated with all NETs is chromogranin A, associated with 99% of metastatic secreting tumors [15]. Most gastroenteropancreatic NETs and many respiratory NETs secrete serotonin. However, reliable assessment of blood serotonin is problematic. Thus, alternatively its main breakdown product, 5-hydroxy-indoleacetic acid (5-HIAA), is measured with a 24h urine collection [16]. Specific biochemical tests should be requested depending on which syndrome is suspected; for example, in our second case, the patient was suspected for having glucagonoma and thus his glucagon levels were tested and found to be higher than normal.

Imaging techniques are necessary once biochemical tests confirm the suspicion for NET. One of the main purpose of imaging is to add information for the staging of disease, which strongly dictates therapeutic options: resection or chemotherapy are planned accordingly [2]. Both conventional imaging and nuclear imaging should be used for primary lesion detection [2]. The choice of first-line imaging technique is dependent on the suspected location of the tumor. In gastrointestinal and pulmonary NETs, endoscopy with ultrasonography (EUS) and biopsy is the first choice [17] for diagnosis, but it must generally be followed by cross-sectional imaging such as CT for accurate staging of disease. CT is also the initial imaging investigation used in patients with a suspected small bowel gastrointestinal NET and pancreatic NET [18]. CT enteroclysis and CT/MRI enterography is useful for demonstrating an occult primary NET in patients with a high level of suspicion [19]. Most NETs are hyper-enhancing during the arterial phase of multi-phase CT. Latest studies have proven how this hyper-enhancement is inversely correlated with the grade of the tumors, being lower in undifferentiated low grade tumors [20]. Other purposes of imaging in NETs are screening of the risk population who have familial syndromes, assessing the extent of disease, and predicting response to treatment.

If CT cannot identify the primary tumor, or when the primary tumor has been detected but whole-body imaging for staging is recommended, somatostatin receptor scintigraphy (SSRS) is recommended with single-photon emission CT (SPECT) or PET/CT [21]. The biologic basis of SSRS is that well-differentiated NETs more often express somatostatin receptors. Thus, radiolabeled somatostatin analogues have been developed wherein the expression of somatostatin receptors is a high predictor of response to treatment. For example, ^{111}In (^{111}In)-octreotide have been shown to be sensitive for detecting NET. However, lesions smaller than one centimeter and high grade tumors with under-expressed somatostatin receptors lower the sensitivity of this technique [22]. Another somatostatin analogue, ^{68}Ga -DOTATOC PET, has been proven to be more sensitive in identifying lesions compared to conventional octreotide scintigraphy [23]. Several other ^{68}Ga -labelled somatostatin analogues are commercially available and share the same biological activity, differing only in the different somatostatin receptors (SSTR) they bind to: DOTA octreotide (DOTATOC) and DOTA octreotate (DOTATATE) bind to SSTR2 and SSTR5, whereas DOTA-NaI-octreotide (DOTANOC) binds to SSTR2, SSTR3, and SSTR5 [24]. All these techniques are highly sensitive and specific: the sensitivity of ^{68}Ga -PET for NETs is >90%, while the specificity ranges from 92 to 98% [24, 25]. ^{68}Ga -PET can be performed in a single day examination, as opposed to the 3 days necessary for ^{111}In -pentetreotide SPECT. The latest studies prove that ^{68}Ga can be marked with the same peptide used for PRRT, making this technique diagnostic and therapeutic at the same time [25]. Finally, in cases where the tumor is poorly differentiated but somatostatin receptors are not expressed, [^{18}F] fludeoxyglucose (^{18}F -FDG) PET/CT can be used instead of SRSS, as well-differentiated NETs are typically not ^{18}F -FDG avid [26].

3.1.3 Case discussion

The first case we presented was a man with gastrinoma and MEN-1 syndrome. MEN-1 syndrome is an uncommon genetic disease that is usually inherited as an autosomal dominant disorder, but can also emerge sporadically. It is associated with several endocrine

and non-endocrine tumors, typically involving the parathyroid glands (>90%), the pituitary gland (15% to 55%), and the pancreas (more than 50%) [27]. Adrenocortical tumors can also be detected and are generally non-functioning. Non-endocrine tumors that may occur in MEN-1 syndrome are facial angiofibromas, collagenomas, lipomas, meningiomas, ependymomas, and leiomyomas [28]. Primary hyperparathyroidism is present in most of the patients and imaging is not usually necessary for the diagnosis, since it is usually multiglandular rather than single lesion. Prolactinomas are the most frequent pituitary tumor, but they can be non-secretory tumors or secrete different types of hormones. The pituitary macroadenomas are the most common type and malignant degeneration is rare. Brain MRI is usually indicated for local staging and follow-up [28]. Neuroendocrine gastroenteropancreatic tumors occur in more than 50% of the patients with MEN-1 and they are usually multiple. Two-thirds of these tumors produce excessive amounts of hormones, including gastrin, insulin, somatostatin, glucagon, neurotensin, or vasoactive intestinal polypeptide. The most common functional tumors are gastrinomas and insulinomas. Pancreas is the most common site of insulinomas and non-functional tumors, whereas gastrinomas are usually located in the duodenal submucosa or in the soft tissues around the pancreas. Gastrinomas in MEN-1 syndrome are usually multiple and half of them present metastasis to the liver and/or lymph nodes before diagnosis. Zollinger-Ellison syndrome is the manifestation of gastrinomas and is characterized by esophagitis, vomiting, epigastric pain, diarrhea, weight loss, and peptic ulcers especially in unusual locations [28].

The second case we presented was a patient diagnosed with malignant pancreatic glucagonoma. Glucagonomas are rare functional pancreatic neuroendocrine tumors (<10%) with an annual incidence of 0.01–0.1 case per 100,000. It arises from islet alpha cells, commonly at the pancreatic tail. Glucagonomas are typically diagnosed in the 5th decade of life, without gender predilection [29, 30]. At presentation, glucagonomas are frequently large (> 5.0 cm) and solitary, and the patients frequently present liver metastasis (50–80%). Other common sites of metastases are regional lymph nodes, bone, adrenal glands, kidney, and lungs. The clinical manifestations are weight loss, skin lesions (necrolytic migratory erythema), diabetes mellitus, anemia, diarrhea, venous thrombosis, and neuropsychiatric symptoms. The first 3 symptoms are the most prevalent, occurring in about 65–90% of the patients [29]. Neurologic symptoms are rarer and include ataxia, dementia, optic atrophy, and myopathy. Glucagonomas can be classified in to 3 groups as following: glucagonomas with skin syndrome, glucagonomas with diabetes, and glucagonomas with multiple syndromes. The physiopathology of the necrolytic migratory erythema remains unknown, although it usually disappears when the serum glucagon levels returns to the normal [30]. On imaging modalities, glucagonomas present significant hypervascularity; however, as it grows necrotic areas appear and reduce the enhancement. The well-differentiated lesions manifest with increased expression of SSTR at the cell membrane and are avid on PET/CT with DOTA-peptides, which can guide the treatment approach. Complete resection of the primary tumor and the metastases remains the curative treatment. The other treatment options include long-acting somatostatin analogues, percutaneous ablation of the metastases, targeted radiotherapy, radioembolization with microspheres, and liver transplantation in rare cases. The prognosis of glucagonomas depends on the stage; however, considering that it is a slow-growing tumor, prolonged survival is observed even in metastatic cases [29].

The third case we presented was a patient with malignant low grade insulinoma. Malignant insulinoma occurs in a small group of patients with insulinoma, 90% of which are benign adenomas. About 85% of patients with functioning insulinoma present with symptoms of hypoglycemia [31]. The incidence of malignant insulinoma is 0,4/1000000 persons [32]. For this reason, there is not a universal consensus on clinical approach and diagnosis workflow. The prognosis of patients with malignant insulinoma is comparably poor, with a mean survival period of 2 years [7]. The metastases occur to the liver for most of cases, and are associated with poor prognosis. Lymph node involvement is not as common as liver metastases and after surgical excision, these patients maintain a prolonged tumor-free survival [33]

The fourth case we presented was a patient with primitive biliary neuroendocrine tumor. The frequencies of primary NETs reported as occurring in the liver or biliary tract is less than 1% of all NETs so it is an extremely rare condition [2]. Primary biliary tract NETs are rare and commonly located in the common hepatic duct and distal bile duct, and occur even more rarely in the intra-hepatic ducts. Therefore, the most common symptoms in those patients are jaundice; however, depending on the localization along the biliary tree, patients can be asymptomatic, as the one that we presented. The main differential diagnosis is cholangiocarcinoma and it is difficult to differentiate them before histologic analysis. However, presence of arterial hyperenhancement with washout in the delayed phase instead of progressive enhancement (common pattern in cholangiocarcinoma) may alert the radiologist to the possibility of uncommon biliary tumors, such as NET. Another feature which could have helped the diagnosis would be the uptake on DOTA-peptide PET/CT, which it was not performed in this patient.

Like the other sites NETs, biliary NETs are classified into (1) well differentiated (low grade, G1), (2) moderately differentiated (intermediate grade, G2), and (3) poorly differentiated (high grade, G3), depending on the appearance, mitotic rate, Ki-67 index, and presence of necrosis. Patients with well-differentiated tumors have a better prognosis with a prolonged survival [34]. So far, surgical resection is still the only curative treatment for biliary NET, resulting in long-term disease-free survival, even in the setting of metastatic liver disease.

The diagnosis of NETs is challenging and generally based on clinical manifestations, blood biochemical tests, imaging techniques, and pathology. Imaging techniques have a pivotal role in staging and treatment planning. It is important for both clinicians and radiologists to be aware of to be aware of these rare tumors and their characteristics.

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Fig. 1.

Case 1: Contrast-enhanced CT which demonstrated multiple hypervascular liver nodules measuring up to 1.5 cm (Figures **A,B,C**; white arrows), 2.5 cm nodule in the pancreatic tail with rim enhancement in the arterial phase (Figure **C**; dashed arrow), bilateral adrenal hypodense nodules (Figures **B,C**; white arrowheads), multiple hyperenhancing lesions in the stomach and duodenum measuring up to 3.0 cm (Figures **A,B,C**; white asterisks), peripancreatic and peri-duodenal lymph nodes, (Figures **C,D**; black arrows). Patient underwent upper endoscopy which demonstrated multiple gastroduodenal mucosal ulcers and nodules (Figure **E**). Pathology for the gastric nodules was consistent with neuroendocrine neoplasm with positive staining for chromogranin and synaptophysin and one in the duodenum was consistent with gastrinoma.

Fig. 2.

Case 2: **A:** CECT shows multiple hypervascular liver masses with central necrosis, measuring up to 14.5 cm (white arrows) and a 4.0 cm nodule in the pancreatic tail (dashed white arrow). **B:** SPECT/CT OctreoScan reveals focal activity in the pancreatic tail consistent with the primary neuroendocrine tumor (white arrow) and extensive octreotide avid masses in the liver corresponding to metastasis (asterisks), which suggest that the lesions have somatostatin receptors. **C:** Biopsy of the liver demonstrates relatively uniform, round tumor cells with stippled chromatin and inconspicuous nucleoli arranged in diffuse sheets or nests, with a low mitotic activity (<1 mitosis/10 high-power fields).

Fig. 3.

Case 3: Contrast-enhanced CT, arterial phase, shows a heterogeneous slightly hypervascular mass in the body\tail of pancreas measuring 3.5 cm (Figure A, open arrow). Multiple bilobar liver metastases (Figure B,C, arrows)

Fig 4.

Case 4: MR demonstrated a 2.2 cm nodule at the confluence of the right hepatic biliary ducts (Figures **AD**, white arrow) resulting in upstream biliary ducts dilatation (Figures **A–D**, white asterisks). The nodule had low signal intensity on fat-suppressed T2WI (Figure **A**) and T1WI (Figure **B**), demonstrated hyperenhancement in arterial phase (Figure **C**) and washout appearance in the delayed phase (Figure **D**). The right lobe also presented transient hepatic attenuation differences in the arterial phase (Figure **C**, arrowheads) due to compression of the right portal vein by the nodule (Figure **D**, dashed arrow). Microscopy demonstrated nodular and diffuse infiltration of round cells with stippled chromatin, inconspicuous nucleoli, and finely granular cytoplasm (Figure **E**, 100x magnification, hematoxylin and eosin). The average mitotic rate was $<2/50$ HPF and the estimated Ki 67 was $<2\%$. Those characteristics were consistent with well-differentiated and low grade neuroendocrine neoplasm. Ten years after the surgery, the patient was asymptomatic and with no evidence of recurrence (Figure **F**).

Table 1

Summary of neuroendocrine tumor cases.

Case	Sex	Age	Symptoms	Past history	Blood tests	Histology	Localization	Metastasis	Lymph nodes	Workup	Imaging features	Outcome
1	M	43	Nausea, vomiting, diarrhea, epigastric pain	Hyper parathyroidism, hypertension, hyperlipidemia	Anemia, elevated serum calcium	Gastrinoma	Stomach, duodenum	Liver, early arterial-phase enhance.	+	CT , endoscopic biopsy	Multiple hyper enhancing lesions in stomach and duodenum	MEN-1 syndrome diagnosed
2	F	68	Diarrhea, fatigue, weakness, abdominal pain, cutaneous rash, weight loss	Diabetes mellitus, hyperlipidemia	AST, ALT, alkaline phosphatase, gamma-glutamyl transferase increased	Malignant glucagonoma	Pancreatic tail	Liver, early arterial-phase enhance.	+	CT , ultrasound-guided biopsy, SPECT-CT OctreoScan with ¹¹¹ In pentetreotide	Pancreatic head lesion, multiple hyper enhancing liver lesions	n/a
3	M	73	Fatigue, dizziness, sweat	Hypo thyroidism, post thyroidectomy for benign goiter	Hypo glycemia	Low grade insulinoma	Pancreatic body\tail	Liver, early arterial-phase enhance.	+	CT, ultrasound-guided biopsy	Heterogeneous pancreatic mass, bilobar liver metastases	n/a
4	M	52	-	Steatosis	AST, ALT, CA 19.9 increased	Primitive biliary neuroendocrine	Right hepatic duct	None	-	MRI, ultrasound-guided biopsy	Nodule at the confluence of the right hepatic biliary ducts resulting in upstream biliary ducts dilatation	Hepatectomy, bile duct resection with cholecystectomy, and Roux-en-Y biliary reconstruction; disease free at 10 y