Epidemiology-Clinical Presentation of Occult Primary Neuroendocrine Neoplasms

Subjects: Oncology

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Neuroendocrine neoplasms (NENs) are rare tumors that originate in diffuse neuroendocrine cells, potentially affecting any organ. NENs encompass a large and heterogenous group of neoplasms characterized by different biological behavior, depending on the clinical and histopathological features and primary site. NENs are classified into well-differentiated G1–G3 NENs and poorly differentiated G3 neuroendocrine carcinomas (NECs), based on their morphological features and proliferation rate. Approximately 11% to 14% of subjects with neuroendocrine neoplasms (NENs) have metastatic lesions with unknown primary origin (UPO), with the majority of UPO-NENs found in the small bowel

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1. Epidemiology

Neuroendocrine neoplasms (NENs) represent around 0.5% of all newly diagnosed neoplasms [1]. In recent decades, the incidence of NENs has hugely increased, likely due to improvements in diagnostic techniques and increased disease awareness [2], being approximately 5.86/100,000 per year [3]. The most frequent primary sites are represented by the gastrointestinal/pancreatic tract (62–67%) and lung (22–27%). In well-differentiated tumors, the majority of metastatic sites are found within the liver only [1].

Approximately 11% to 14% of subjects with NENs present metastatic lesions with a UPO, being the majority of UPO-NENs found in the small bowel [4], particularly for well-differentiated forms, followed by the pancreas. Conversely, in poorly differentiated forms, the primary site is generally located in the lung [5]. In 2020, Abdel-Rahman et al. [6] conducted a real-world, population-based study to evaluate the actual incidence and outcome of UPO-NENs. Out of a total of 51,415 recorded cases with NENs, a total of 3550 cases (7%) were diagnosed with UPO-NENs. The authors observed first that the diagnosis of UPO-NENs has increased across the past 4 decades; furthermore, they reported that metastatic small-intestinal NENs appear to have a better prognosis when compared with metastatic UPO-NENs (for both carcinoid tumors and neuroendocrine carcinomas).

2. Clinical Presentation

In the neuroendocrine setting, the majority of symptoms are non-specific and tend to overlap with more common, often gastro-intestinal (GI), conditions, leading to a significant delay in diagnosis. This assumption is particularly true for those cases in which the primary lesion is undetectable thorough conventional imaging techniques [computed tomography (CT) scan, magnetic resonance imaging (MRI)], and the diagnosis of NENs may be, therefore, mistakenly shelved in favor of other endocrine or GI disorders contributing to the aforementioned diagnostic delay.

Clinical features may be related to the tumor's hormonal production (functioning NENs), to the site of the primary tumor or to its metastases (mostly hepatic). Functioning NENs can be responsible for many renowned clinical syndromes (as depicted in **Table 1**), while non-functioning forms' presentation is often connected to their mass effect.

Table 1. Functioning neuroendocrine neoplasms and their associated clinical syndromes.

Insulinoma	**Whipple's triad** • Hypoglycemia (<50 mg/dL) • Hypoglycemic symptoms (dizziness, sweating, confusion, increased HF) • Symptoms' resolution with glucose ingestion
Gastrinoma	**Zollinger Ellison Syndrome** • Peptic ulcer disease • Diarrhea • Gastro-esophageal reflux disease • Weight loss
VIP-oma	**Verner Morrison Syndrome** • Watery diarrhea • Dehydration • Hyperkalemia
Glucagonoma	• Diarrhea • Glucose intolerance/diabetes

	• Necrolytic migratory erythema • Weight loss and steathorrhoea • Anemia
Somatostatinoma	• Diarrhea • Weight loss • Diabetes • Gallstones

r 12–22% [7]

In this scenario, frequent local symptoms include: bowel obstruction or perforation (as a matter of fact, small-bowel NENs are often identified during emergency abdominal surgery), obscure intestinal bleeding without any significative endoscopic finding, unexplained anemia from chronic blood loss or, rarely, obstructive manifestations from vascular compression. Likewise, occult bronchial NENs can be responsible for hemoptysis, dyspnea or recurrent infections due to bronchial obstruction.

The presence of liver metastases can be symptomatic itself by causing abdominal pain (due to liver-capsule stretching or bleeding) or mixed hyperbilirubinemia (as a result of both obstruction and hepatic failure) up to obstructive jaundice. In addition, liver metastases—whether detectable through conventional imaging or not [8]—can be responsible for the development of carcinoid syndrome (CS), a clinical syndrome characterized by flushing, diarrhea and bronchospasm as leading symptoms that can lead to life-threatening complications, such as carcinoid heart disease. The prevalence of CS in patients with NENs has grown significantly in the past decade together with the well-known increase in NENs' incidence: a large American study showed an increase in its incidence from 11% to 19% during the decade 2000–2011 and its association mainly to midgut NENs (40%); moreover, the presence of CS seemed to be linked to a shorter overall survival [9]. In the setting of UPO-NENs, CS can represent the first or the only clinical manifestation (especially if the primary tumor has a small size), but, again, its symptoms can be mistaken for other conditions (including anxiety, irritable bowel syndrome, menopause, allergic asthma) and the presence of liver metastases frequently ends up being an incidental finding. It is, indeed, a common experience that the diagnosis of NENs is generally delayed and patients with small-bowel NENs are often erroneously diagnosed with irritable bowel syndrome or inflammatory bowel disease due to the non-specific clinical presentation.

3. Diagnostic Work-Up

Localization of midgut tumors might be challenging due to their usually small size. Early localization of the primary site is a fundamental prerequisite for improving the patient's management and prolonging survival [10], especially for patients with well-differentiated NENs.

A continuum of investigations to identify the primary tumor is warranted. A multimodal imaging approach, including CT, MRI, positron emission tomography (PET) and somatostatin receptor scintigraphy (SRS) together with endoscopy, is often necessary for detecting the primary tumor [11][12]. In addition to conventional upper and lower GI endoscopy, more sophisticated techniques, including CT enterography, CT angiography, video capsule endoscopy or double-balloon enteroscopy and endoscopic ultrasonography, may all be combined to shed light on challenging cases [12][13]. In selected cases, whenever all the available diagnostic tools have failed, surgical exploration may be warranted. In this setting, an open exploration is considered to be superior to laparoscopy when the primary site cannot be identified but the data are limited [13][14]. However, despite surgical exploration, the primary site is not found in approximately 13% of the cases [12].

The presence of a functional syndrome might be of help to identify the site of the primary lesion in UPO-NENs. In fact, CS is typically secondary to an NEN located in the small bowel and, in this setting, 5-hydroxyindoleacetic acid (5-HIAA) urine levels should be determined, being the specific biomarker for CS [15]. On the other hand, when a functioning NEN as a gastrinoma is suspected, the primary lesion is generally small in size, difficult to be detected and often located at an anatomic region known as the gastrinoma triangle [16]. In the presence of paraneoplastic syndrome, including ectopic ACTH syndrome, a primary tumor located in the lung, the thyroid (medullary carcinoma) or associated with a gastrinoma should be suspected [17]. However, specific biomarkers for UPO-NENs are still lacking.

In clinical practice, the first sign of a neoplastic process secondary to a UPO-NEN is the detection of liver metastases via conventional radiology (i.e., CT scan). Additional work-up, such as upper and lower GI endoscopy, chest CT and MRI of the abdomen, should be required. Conventional radiology might fail to detect the primary tumor in the pancreas or small bowel when the lesions are small or the tests are performed using a suboptimal protocol [18].

3.1. Pathology

In patients with UPOs, immunohistochemical markers are useful for cell-type determination and pathologic diagnosis.

UPO-NENs are most often well-differentiated grade 1 or 2 tumors which commonly originate from the intestinal or pancreatic system (approximately 60–65% of cases) or lungs (approximately 20–25%) [1][19]. Liver metastases dominate in the clinical setting, and these lesions are usually reachable using a core-needle biopsy (CNB), as current guidelines strongly recommend; however, occasionally, focal liver resections might be necessary to obtain sufficient material [20].

Morphological, immunohistochemical and molecular analyses are equally essential in the assessment of NENs. NENs may exhibit variable growth patterns and cellular characteristics easily identifiable on routine hematoxylin–eosin staining alone [21][22]. For instance, while metastatic NENs with a primary tumor located in the stomach and duodenum may demonstrate a glandular-like pattern, and SI-NENs often exhibit an organoid or nested growth pattern; in contrast, pancreatic and rectal NENs may present with a ribbon-like or trabecular architecture. To identify the actual origin of a UPO-NEN, a wide variety of immunohistochemical markers may be assessed. These include classic markers such as Chromogranin A (CgA) and Synaptophysin (SYP) or INSM1 [23] to confirm the neuroendocrine differentiation [24][25]. CDX2 is a transcription factor, a useful marker of intestinal NENs and, because of its association with GI differentiation, it is also found in gastrin-positive pancreatic NENs and colorectal adenocarcinoma [26][27]. In the setting of WDNENs, Thyroid Transcription Factor1 (TTF1) positivity may suggest a bronchial primary in 43% of the cases. However, it is not specific in poorly differentiated lung neuroendocrine carcinomas (PDNECs), as it is also present in 50% of small-cell tumors at other sites [26][28][29]. Islet-1 (ISL1) can be used as a marker for pancreatic origin [30][31]. Serotonin, associated with CDX2 and SATB2, has utility in identifying EC tumors originating in the ileum or appendix [32][33]. Colorectal NENs may present with positive staining for glucagon-like peptide 1, CDX2 and SATB2 [31][34]. Pheochromocytomas and abdominal paragangliomas stain positive for neuroendocrine markers CgA, SYP, ISL1, INSM1 and, often, GATA3; subsets of cases may display an intricate network of supporting sustentacular cells which are highlighted by an S100 or SOX10 stain [35]. Paranuclear dot-like staining for CgA, CK20 and Neurofilament (NF), and polyomavirus stain, may also help in the identification of neuroendocrine skin lesions such as Merkel cell carcinomas (MCCs) [36][37]. Therefore, to successfully identify UPO-NENs, a combined assessment using clues from clinical history, radiology, morphology and immunohistochemistry is recommended, rather than blind trust in a single marker [7][38]. The interaction between physicians and pathologists is, therefore, fundamental.

3.2. Functional Imaging

Somatostatin receptor scintigraphy (SRS) has been extensively used for the initial staging of disease and to evaluate somatostatin receptor (SSTRs) status; furthermore, it has been explored to detect occult primary sites in patients with metastatic gastro-entero-pancreatic (GEP) NENs with a detection rate of 39%. However, 68GaDOTANOC positron emission tomography (PET)/CT has proved to be more accurate and generally represents the functional imaging of choice, being able to also detect very small lesions [39]. According to previous experiences, Ga-68-DOTANOC PET/CT helped in the detection of undiagnosed primary sites in patients with metastatic NENs in a percentage ranging from 45.5% [40] to 59% of the patients [41][42].

A recent meta-analysis [43], including 10 studies of a total of 484 patients with UPO-NENs, demonstrated the high diagnostic sensitivity of 68Ga-DOTA-SSTR for UPO-NENs. 68Ga-DOTA-SSTR PET/CT was highly effective in locating the primary and metastatic sites of UPO-NENs, with a pooled detection rate of 61%.

Fluorodeoxyglucose PET may be employed for the detection of occult primary sites in case of high-grade histology (G3 NEN), whereas F-DOPA and MIBG imaging may be employed in selected cases, especially when paraganglioma/pheochromocytoma are suspected.

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