Review Article

Diffuse Endocrine System and Paragangliomas: Pathology, Predictive Biochemistry and Genetics

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Keywords:
Carcinoid,
Neuroendocrine carcinoma

Abstract
Neuroendocrine tumors (NETs) of the diffuse neuroendocrine system (neuroendocrine cells spread as a single cell or as clusters of cells throughout the gastrointestinal tract, the bronchopulmonary system, and the urogenital tract), are often referred to as carcinoids. Neuroendocrine tumors may present a considerable diagnostic and therapeutic challenge as their clinical presentation is nonspecific and usually late, when metastases are already evident. Tumors of the diffuse neuroendocrine system represent a significant and increasing clinical problem, and there is a need to develop both early diagnostic tests as well as to establish targeted therapeutic strategies.

1. Introduction
Neuroendocrine tumors (NETs) of the diffuse neuroendocrine system (neuroendocrine cells spread as a single cell or as clusters of cells throughout the gastrointestinal tract, the bronchopulmonary system, and the urogenital tract), are often referred to as carcinoids. NETs occur most frequently in the gastrointestinal tract (66%), with the second most common location in the bronchopulmonary system (31%), followed by less frequent locations including the ovaries, testes, hepatobiliary system, and pancreas [3]. Carcinoids can be either sporadic (nonfamilial) or part of familial syndromes such as multiple endocrine neoplasia, von Hippel–Lindau syndrome, and neurofibromatosis [5]. The tumors tend to be slow-growing, small (although aggressive variants exist) and often present a considerable diagnostic and therapeutic challenge due to lack of symptoms until they metastasize. The majority of tumors are thus diagnosed at a stage at which the only curative treatment, radical surgical intervention, is no longer an option. Long-acting somatostatin analogues are often effective in ameliorating symptoms but have no effect on tumor growth, and specific tumor-targeted treatments are thus frequently used, a tumour curative strategy. As many as 15–25% of NETs exhibit a synchronous or metachronous association with other tumors (usually adenocarcinomas, commonly located in the colon) [6]. This probably reflects the activity of growth factors produced by the tumors that promote phenotypic changes in susceptible cells and induce neoplastic transformation [6,7]. Although large percentage of gastrointestinal NETs are multicentric (2% overall but as high as 33% in the small bowel), supporting the thesis that a common local growth factor or initiating event may influence similar progenitor cells in different locations [4,8].

2. Risk factors for neuroendocrine cancer
- People with multiple endocrine neoplasia type 1 (MEN 1) syndrome develop multiple endocrine and neuroendocrine tumors.
- Multiple endocrine neoplasia type 2 (MEN 2) syndrome is associated with many endocrine tumors, such as pheochromocytoma. A tumor that starts in an adrenal gland (the glands on top of each kidney that release hormones to help control heart rate and blood pressure) and medullary thyroid carcinoma.
- Von Hippel-Lindau syndrome is an inherited familial cancer syndrome. People with this disorder may develop a variety of neuroendocrine tumors, including pheochromocytoma and pancreatic endocrine (islet cell) tumors.
- Tuberous sclerosis is a genetic disorder that causes benign tumors to form in many organs of the body, including the eyes, skin, brain, lungs, heart and kidneys. People with tuberous sclerosis also have an increased risk of developing neuroendocrine tumors.

Neurofibromatosis:
A genetic condition that affects the nervous system. It affects the development and growth of neurons (nerve cells), causes tumours (neurofibromas) to grow on nerves and may produce other abnormalities in muscles, bones and skin. type 1 (von Recklinghausen disease) causes many neurofibromas (benign tumours that form in nerves) to occur. Neuroendocrine tumours of the pancreas and small intestine are more common in people diagnosed with neurofibromatosis type 1. Tobacco smoke- Small cell lung cancer (SCLC) and large cell neuroendocrine carcinoma (LCNEC) are neuroendocrine carcinomas that develop in the lungs. These tumours are strongly associated with tobacco smoking. Neuroendocrine tumours of the larynx may also be associated with tobacco smoke. Some types of neuroendocrine tumours are more common in people with a family history of neuroendocrine tumours or other types of cancer.

3. Classification
The traditional classification of carcinoids, based on their embryonic origin, comprises the foregut (lung, thymus, stomach, pancreas and duodenum), midgut (from the duodenum beyond the Treitz ligament to the proximal (transverse colon) and hindgut carcinoids (distal colon and rectum) [9]. Although this archaic classification is still used, a tumor-based classification introduced by the World Health Organization in 2000 has far greater applicability [10]. The latter classification utilizes the more generic term, neuroendocrine tumor, and tumor classification is based upon size, proliferative rate, localization, differentiation and hormone production. Distinction is made between well differentiated NETs (benign behaviour or uncertain malignant potential), well differentiated neuroendocrine carcinomas (low-grade malignancy), and poorly differentiated (usually small cell) neuroendocrine carcinomas of high-grade malignancy. The term carcinoid was not completely discarded, and it is used synonymously.
with the term ‘well differentiated NET’. The current basis of lung NET classification produced by the World Health Organization (2004) is a histological classification system comprising four subtypes of tumors: the low-grade typical carcinoid, the intermediate-grade atypical carcinoid (both classified as bronchopulmonary carcinoids), and the two high-grade large-cell neuroendocrine carcinoma and small-cell lung carcinoma.

The World Health Organization diagnostic criteria for a typical carcinoid are: a tumor with carcinoid morphology and less than 2 mitoses/2mm² (10 HPH), lacking necrosis and 0.5 cm or larger. An atypical carcinoid is defined as a tumor with carcinoid morphology with 2–10 mitoses/2mm² and/or necrosis (often punctate).

4. Clinical manifestations

In hormonally active tumors, variable symptoms may develop depending on the tumor cell of origin and the effects of secreted bioactive substances (serotonin, catecholamine, dopamine, histamine, gastrin, glucagon, prostaglandins, among others). The classical carcinoid syndrome is relatively uncommon (20% of small bowel NETs, <5% for NETs of other locations), typically consisting of diarrhea, cutaneous flushing, broncho-constriction. Gastrointestinal NETs may present with emergency clinical symptoms (3–5%) such as acute abdomen (obstruction, perforation, bleeding) and abdominal angina (major vessel compromise), which arise due to local tumor mass effects or tumor-induced fibrosis. The majority of patients, 50% with bronchopulmonary carcinoids, are symptomatic at presentation, and the most common symptoms are cough (32%), hemoptysis (26%), and pneumonia (24%) (the classical triad) – represent the effects of luminal obstruction and ulceration of the tumor. Cushing’s syndrome may occur as a paraneoplastic phenomenon (ectopic production and secretion of adrenocorticotrophic hormone) associated with bronchopulmonary carcinoids in approximately 1–2% of patients.

5. Biochemical markers

Measurement of urinary 5-hydroxyindole-3-acetic acid, the degradation product of serotonin, has a specificity of 88% for serotonin-producing NETs, although tryptophan-rich foods (bananas, avocados, plums, eggplant, tomatoes, plantain, pineapples and walnuts) can provide false elevations. Overnight 5-hydroxyindole-3-acetic acid collection may be as sensitive as a 24-h collection in identifying patients with serotonin-producing tumors. Higher concentrations of urinary 5-hydroxyindole-3-acetic acid are consistent with a worse prognosis. Chromogranin A is a water-soluble acidic glycoprotein stored in the secretory granules of NETs and can be utilized as a general plasma tumor marker for gastrointestinal NETs as well as ‘nonfunctioning’ tumors. Although plasma chromogranin A levels are very sensitive (99%) markers of NETs, they are nonspecific as they are also elevated in other tumor types, such as small-cell lung carcinoma, and even some prostate carcinomas. In addition to the diagnostic value, however, plasma chromogranin A levels are also well correlated to tumor volume and burden.

Recent studies suggest that alkaline phosphatase and neurokinin A are better predictors of survival in metastatic NETs than chromogranin A. Other markers including serotonin, histamine, gastrin, vasoactive intestinal peptide, glucagon, bradykinin, substance P, neurotensin, human chorionic gonadotrophin, neuroepiteli K, neuroepiteli D and pancreatic polypeptide are of value in precisely defining the functionality of individual NETs. Histochemical indicators of prognosis include the degree of expression of the proliferation marker Ki-67 and the p53 tumor suppressor protein.

6. Topographic localization

Upper gastrointestinal endoscopy can identify lesions to the level of the ligament of Treitz, and colonoscopy can detect terminal ileal tumors as well as colon and rectal NETs. Endoscopic ultrasound is a highly sensitive method for diagnostic and preoperative evaluation of NETs of the stomach, duodenum, pancreas and rectum since it not only identifies submucosal lesions but it also facilitates staging. Flexible fiberoptic bronchoscopy is the most effective technique for the diagnosis and treatment of a variety of bronchopulmonary carcinoids and tumor-targeted radioactive treatment with radiolabeled somatostatin analogues. Positron emission tomography (PET) detects accumulation of radiolabeled biological substances such as 18F-fluorodeoxyglucose and the radiolabeled precursor of serotonin synthesis, 11C-5-hydroxytryptophan.

Neuroendocrine tumours of the endocrine system

These tumors start in the neuroendocrine cells of various endocrine glands: Pituitary adenoma, thyroid medullary carcinoma, thymus neuroendocrine cancer, parathyroid neuroendocrine cancer, pheochromocytoma, paraganglioma.

Neuroendocrine tumours of unknown primary

Most people diagnosed with neuroendocrine carcinoma of unknown primary (CUP) have advanced disease. They will need aggressive treatment to reduce the tumors as much as possible. Rarely, neuroendocrine carcinomas can occur elsewhere in the body, including the breast, kidney, urinary bladder and prostate. Other rare neuroendocrine disorders include multiple endocrine neoplasia (MEN) syndromes - genetic disorders that usually cause multiple tumours to develop in the endocrine glands. Once the type of tumour has been diagnosed, the doctor will also consider: the functional status (if the tumour is releasing hormones or not) and type of hormone released, the frequency and severity of symptoms caused by too much of a particular hormone, the grade of the tumour (how abnormal the cancer cells look and behave), the stage of the cancer, including if it has spread (metastasized) and where it has spread, evidence of any complications, such as carcinoid-related heart disease, prognostic factors (special characteristics that might influence the course of the disease), survival statistics for the particular type and stage of cancer.

7. Laryngeal Neuroendocrine Cancers

Benign-Laryngeal paraganglioma

Malignant:

- Typical carcinoid (well diffd), Atypical carcinoid (Mod diffd), Small cell neuroendocrine (poorly diffd), Combined small cell neuroendocrine carcinoma, Large cell neuroendocrine carcinoma

Salivary gland:

1. Neuroendocrine type
   a) Merkel cell subtype
   b) Pulmonary subtype

2. Ductal type

Gastrointestinal and pancreatic neuroendocrine tumours and carcinomas

Gastrointestinal and pancreatic neuroendocrine tumours are together called gastroenteropancreatic (GEP) neuroendocrine tumours. This is the largest group of neuroendocrine tumours and includes: well-differentiated neuroendocrine tumours, well-differentiated neuroendocrine carcinoma, poorly differentiated neuroendocrine carcinoma. They can develop in the following areas of the gastrointestinal tract: pancreas, small intestine, appendix, large intestine (colon and rectum), stomach, esophagus (rare site of neuroendocrine tumours).
Gastrointestinal and pancreatic neuroendocrine tumours and carcinomas are named based on the type of cell they develop in and the hormones the tumours produce: serotonin-producing neuroendocrine tumours or carcinomas, insulinoma, gastrinoma, VIPoma, glucagonoma, somatostatinoma, ACTHoma, PPoma and non-functioning.

**Gastric neuroendocrine tumors**

Gastric NETs account for <2% of all gastric malignancies, 9% of NETs, and the incidence/prevalence is increasing [2].

<table>
<thead>
<tr>
<th>Type</th>
<th>Gastritis of corpus</th>
<th>Zollinger Ellison (MEN1)</th>
<th>None sporadic</th>
<th>Gastric parietal cell acid secreting dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preexisting condition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypergastrinemia</td>
<td>Present</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carcinoid tumors</td>
<td>Small &lt;1.5ccm</td>
<td>&gt;1.5 cms</td>
<td>Large</td>
<td></td>
</tr>
<tr>
<td>Distant liver mets</td>
<td>2-5</td>
<td>10</td>
<td>22-75</td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>Never fatal</td>
<td>Rarely fatal</td>
<td>25% Mortality</td>
<td></td>
</tr>
<tr>
<td>E cell hyperplasia or dysplasia</td>
<td>present</td>
<td>present</td>
<td>absent</td>
<td></td>
</tr>
<tr>
<td>Background mucosa</td>
<td>CAG, intestinal metaplasia</td>
<td>Hypertrophy oxyntic glands, hyperplastic parietal cells</td>
<td>normal</td>
<td></td>
</tr>
<tr>
<td>Clinical management</td>
<td>Endoscopic polypectomy</td>
<td>Endoscopic polypectomy</td>
<td>Gastrectomy</td>
<td></td>
</tr>
</tbody>
</table>

**8. Neuroendocrine lung neoplasms**

1) Well differentiated neuroendocrine carcinoma Old name Carcoid, Kulchitsky tumor, typical carcinoid.

**Features**: Prominent neuroendocrine organoid pattern, No cytologic atypia, Stippled salt pepper chromatin, Low mitotic activity, absence of tumor cell necrosis, neuroendocrine markers strong. These tumours account for 80%–90% of all carcinoid lung tumours. They can develop near the centre of the lung (known as central carcinoids) or toward the edges of the lung (known as peripheral carcinoids). Typical carcinoid tumours are well-differentiated endocrine tumours that are benign or potentially malignant. They grow slowly but sometimes (in about 5% of cases) metastasize to the lymph nodes in the lung. They rarely spread to other lymph nodes or outside the chest.

2) Moderately differentiated neuroendocrine carcinoma Atypical Carcoid.

**Features**: preservation of neuroendocrine growth pattern, increased cytologic atypia, prominent nuclei, Moderately increased mitotic activity, frequent areas of comedonecrosis, retained expression of NE markers.

3) Poorly differentiated neuroendocrine carcinoma. Old name- small cell carcinoma, oat cell carcinoma, kulchitsky cell carcinoma, Large cell neuroendocrine carcinoma, undifferentiated small cell carcinoma.

**Features**: Poorly developed neuroendocrine growth pattern, marked cytologic atypia, small or large cell morphology, High mitotic activity (>10 per 10 HPF), Extensive areas of necrosis.

Small cell lung cancer (SCLC)-SCLC is also known as oat cell carcinoma and small cell carcinoma. It accounts for 15%–20% of all lung cancers. It has a strong association with tobacco smoking. Small cell lung cancer is the most aggressive of all lung cancers, and it usually progresses rapidly. SCLC shows neuroendocrine features, such as producing hormones that can cause signs and symptoms of disease outside the chest (called paraneoplastic syndrome paraneoplastic syndrome). A group of symptoms that occurs when substances released by cancer cells disrupt the normal function of nearby or distant organs or tissues.

Large cell neuroendocrine carcinoma (LCNEC)-LCNEC is a variant of large cell lung cancer, which is a type of non–small cell lung cancer. It is an aggressive type of neuroendocrine lung cancer.

**Other Neuroendocrine lung tumors**

Pulmonary paraganglioma, 10 Pulmonary PNETs. Rare only three cases in literature. Small blue tumour, CD99 t11; 22 translocations.

**9. Conclusion**

In contradiction to the general assumption that NETs/carcinoids are extremely rare and benign slow-growing tumors, it is evident that they are far more common than previously thought and often display a poor prognosis due to widespread disease. Although diagnostic modalities such as SRS, PET and the combination of nuclear imaging techniques with anatomical imaging are useful inaccurate and early diagnosis, the critical requirement is the development of a plasma or genetic marker to predict or identify early lesions. Treatment with somatostatin analogues can palliate symptoms and possibly delay progression, but more efficient therapies are needed to regulate NET cell proliferation. Peptide receptor radiotherapy with somatostatin analogues can palliate symptoms and possibly delay progression, but more efficient therapies are needed to regulate NET cell proliferation. Peptide receptor radiotherapy with somatostatin analogues have demonstrated either minimal or limited efficacy. Contrary to the general assumption that NETs/carcinoids are extremely rare and benign slow-growing tumors, it is evident that they are far more common than previously thought and often display a poor prognosis due to widespread disease. Although diagnostic modalities such as SRS, PET and the combination of nuclear imaging techniques with anatomical imaging are useful inaccurate and early diagnosis, the critical requirement is the development of a plasma or genetic marker to predict or identify early lesions. Treatment with somatostatin analogues can palliate symptoms and possibly delay progression, but more efficient therapies are needed to regulate NET cell proliferation. Peptide receptor radiotherapy with somatostatin analogues have demonstrated either minimal or limited efficacy. Contrary to the general assumption that NETs/carcinoids are extremely rare and benign slow-growing tumors, it is evident that they are far more common than previously thought and often display a poor prognosis due to widespread disease. Although diagnostic modalities such as SRS, PET and the combination of nuclear imaging techniques with anatomical imaging are useful inaccurate and early diagnosis, the critical requirement is the development of a plasma or genetic marker to predict or identify early lesions. Treatment with somatostatin analogues have demonstrated either minimal or limited efficacy.

**References**


