Pancreatic Neuroendocrine Tumors

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KEYWORDS

• Well-differentiated pancreatic neuroendocrine tumor • Pancreatic neuroendocrine carcinoma • Pathologic features • Morphologic variants • WHO classification • Differential diagnosis • Prognosis • Ki67

Key points

- Pancreatic neuroendocrine neoplasms are classified into well-differentiated pancreatic neuroendocrine tumor (PanNET) and pancreatic neuroendocrine carcinoma (NEC) with well-differentiated PanNET accounting for most neoplasms.
- Although most well-differentiated PanNETs are well-circumscribed and hypercellular lesions composed of uniform tumor cells showing salt-pepper chromatin and arranged in different patterns, a number of morphologic variants have been described.
- Several immunohistochemical markers can be used to differentiate pancreatic neuroendocrine neoplasms from other pancreatic primaries or metastatic carcinomas from other origins; however, there are no specific markers that can be used to differentiate pancreatic neuroendocrine neoplasms from neuroendocrine neoplasms of other sites.
- NECs are uniformly deadly, but well-differentiated PanNETs have variable prognosis. Ki67 is the only prognostic marker routinely used in clinical practice.

ABSTRACT

Pancreatic neuroendocrine neoplasms include well-differentiated pancreatic neuroendocrine tumors (PanNETs) and neuroendocrine carcinomas (NECs) with well-differentiated PanNETs accounting for most cases. Other pancreatic primaries and metastatic carcinomas from other sites can mimic pancreatic neuroendocrine neoplasms. Immunohistochemical studies can be used to aid in the differential diagnosis. However, no specific markers are available to differentiate PanNETs from NETs of other sites. Although NECs are uniformly deadly, PanNETs have variable prognosis. Morphology alone cannot predict the tumor behavior. Although some pathologic features are associated with an aggressive course, Ki67 is the only prognostic molecular marker routinely used in clinical practice.

OVERVIEW

Pancreatic neuroendocrine tumors (PanNETs) represent up to 2% of all pancreatic neoplasms. After pancreatic ductal adenocarcinoma they are the second most common primary pancreatic malignancy. There has been a gradual increase in incidence over the past 40 years, with annual incidence among the general population of less than 1 per 100,000 persons per year.[1–3] They are seen only slightly more frequently in men compared with women and in African American as compared with white individuals. Most occur sporadically in adults between the sixth and eighth decades;

Disclosure Statement: There is no conflict of interest for both authors.
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Surgical Pathology ■ (2016) ■–■
http://dx.doi.org/10.1016/j.path.2016.05.006
1875-9181/16/$ – see front matter

Table 1
Hereditary syndromes associated with pancreatic neuroendocrine tumor (PanNET)

Syndrome	Gene Involved	Clinical Presentations	Frequency of PanNET	Clinicopathologic Features
Multiple endocrine neoplasia, type 1	*MEN-1*	Hyperplasia/neoplasms in the parathyroid, pituitary, pancreas, and duodenum	Up to 100%	Nonfunctional or functional (insulinoma: most common functional tumor); gastrinoma (always in the duodenum)
von Hippel Lindau	*VHL*	Pheochromocytoma, hemangioblastoma, clear-cell renal cell carcinoma, pancreatic tumors (PanNETs and serous cystadenoma), and tumors of the middle ear and epididymis	11%–17%	Nonfunctional only; can be clear-cell PanNETs (need to be differentiated from metastatic renal cell carcinoma or solid serous cystadenoma)
Neurofibromatosis type 1	*NF-1*	Café-au-lait macules, neurofibromas, skin-fold freckling, iris Lisch nodules, and bony dysplasia	Rare	Nonfunctional or functional; mostly ampullary somatostatinoma
Tuberous sclerosis	*TSC1* *TSC2*	Hamartomas, disabling neurologic disorders, and dermatologic findings	2%	Nonfunctional or functional

however, PanNETs associated with syndromes, for example, multiple endocrine neoplasia (MEN) 1 and Von Hippel Lindau (VHL), do occur in younger patients.[1] There are 4 well-established hereditary syndromes associated with PanNETs (**Table 1** and further discussed in the article see Pittman ME, Brosens LA, Wood LD: Genetic Syndromes with Pancreatic Manifestations, in this issue).

PanNETs are classified as functional when associated with hormone secretion and a clinical syndrome (**Table 2**) or nonfunctioning. More than 50% of PanNETs are nonfunctional in contemporary studies.[4] PanNETs measuring smaller than 0.5 cm are referred to as pancreatic neuroendocrine microadenomas and are by definition nonfunctional.[5] They are more frequently encountered in the setting of MEN1.[6]

The 2010 World Health Organization (WHO) classification divides the tumors into 3 grades (**Table 3**): grade 1 and 2 are classified as well-differentiated neuroendocrine tumors (NETs), and grade 3 is regarded as neuroendocrine carcinoma (NEC). The latter is further classified as small-cell or large-cell neuroendocrine carcinoma.

Table 2
Four most common functional pancreatic neuroendocrine tumors

Pancreatic Neuroendocrine Tumor	Incidence (million/y)	Hormone	Syndrome	Clinical Behavior
Insulinoma	1–3	Insulin	Vasomotor symptoms, low blood sugar, and reversal of symptoms by glucose administration	Indolent
Gastrinoma	0.1	Gastrin	Complicated and uncomplicated gastric/duodenal ulcers	Can be aggressive
VIPoma	0.05–0.2	VIP	Large-volume secretory diarrhea causing dehydration and electrolyte disturbances	Mostly aggressive
Glucagonoma	0.01–0.1	Glucagon	Glucose intolerance, weight loss, and necrolytic migratory erythema	Mostly aggressive

Abbreviation: VIP, vasoactive intestinal polypeptide.