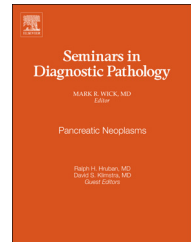


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Pancreatic neuroendocrine tumors: Pathologic and molecular characteristics



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ABSTRACT

Pancreatic neuroendocrine neoplasms include mainly well-differentiated neuroendocrine tumors but also rare poorly differentiated neuroendocrine carcinomas. Molecular mechanisms underlying pancreatic neuroendocrine tumorigenesis have recently been elucidated. While alterations in the chromatin remodeling and PI3K/Akt/mTOR pathways are present in most well-differentiated pancreatic neuroendocrine tumors, mutations in TP53 and RB may contribute to the development of pancreatic poorly differentiated neuroendocrine carcinomas. With these discoveries, new molecular targeted therapies have become available and show promise in some patients with pancreatic well-differentiated neuroendocrine tumor.

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Introduction

Pancreatic neuroendocrine neoplasms, including well-differentiated neuroendocrine tumors (PanNETs) and poorly differentiated neuroendocrine carcinomas (NECs), are malignant neoplasms with significant neuroendocrine differentiation. Although rare, they are the second most common neoplasm of the pancreas, accounting for approximately 5% of all pancreatic malignancies. The annual incidence is less than 1 per 100,000 persons per year in the general population^{1–4}; however, autopsy studies have shown a much higher prevalence.⁴ In addition, the incidence of PanNETs has steadily increased over the last 40 years,^{1,3} partly due to increased awareness of these tumors among clinicians and widespread use of modern imaging techniques.

According to the World Health Organization (WHO) 2010 classification of digestive neuroendocrine tumors, neuroendocrine neoplasms of the pancreas are divided into three

grades: well-differentiated PanNET WHO grade 1, well-differentiated PanNET WHO grade 2, and poorly differentiated pancreatic NEC WHO grade 3.⁵ The vast majority of pancreatic neuroendocrine neoplasms are well-differentiated PanNETs. PanNETs can be classified based on clinical symptoms into functional and nonfunctional tumors, with nonfunctional tumors accounting for more than 50% of the total cases in contemporary studies. While most PanNETs occur sporadically, some are associated with a genetic syndrome, such as the multiple endocrine neoplasia type 1 (MEN1) and von Hippel-Lindau (VHL) syndromes.⁶

Surgery is the only curative treatment for PanNETs and is recommended only when complete resection is possible. However, more than half of patients present with distant metastatic disease at initial diagnosis,³ and most PanNETs are incurable once they have metastasized. Although PanNETs are associated with a much better prognosis compared to pancreatic ductal adenocarcinoma, the 5-year survival rate

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is still less than 40%.^{1,3} With recent discoveries in PanNETs, new molecular targeted therapies have become available and show promise in some patients with PanNETs. In this review, we discuss the clinical, pathologic, and molecular characteristics of PanNETs.

Clinical features

Most patients with PanNETs are in the sixth and seventh decade of life, with a slight male predominance.^{1,2} Nonfunctional PanNETs are not associated with a hormone hypersecretion syndrome, nonetheless these tumors secrete a number of substances, such as pancreatic polypeptide and chromogranin, and may secrete hormones at levels insufficient to cause symptoms.⁷ Due to lack of specific symptoms, nonfunctional PanNETs tend to be diagnosed at more advanced stages, with a large primary tumor, invasion to adjacent organs, or distant metastases, compared with functional PanNETs such as insulinomas.³ However, with increasing numbers of PanNETs being discovered incidentally, more patients with nonfunctional PanNETs are being diagnosed at an early stage.

Nine well-established syndromes have been described to be associated with functional PanNETs. Insulinoma is considered the most common functional tumor, followed by gastrinoma, VIPoma, and glucagonoma (Table 1). Other rare functional PanNETs with a well-defined syndrome include somatostatinoma, GRHoma, ACTHoma, PanNET-causing carcinoid syndrome, and PTHrP-oma.^{8,9} These tumors secrete a specific hormone that causes a characteristic clinical syndrome. While most insulinomas are associated with an indolent clinical course, other functional tumors, such as the glucagonoma, are mostly aggressive.

Genetic syndromes

While most PanNETs are sporadic, some of them occur in patients with an underlying genetic syndrome, including the

MEN-1 syndrome, VHL syndrome, neurofibromatosis type 1 (NF-1), and tuberous sclerosis complex (TSC). Table 2 outlines their inheritance pattern, the specific gene involved, and clinical features of these syndromes. The occurrence of PanNETs in patients with these genetic disorders raises the potential that these same genes may be involved in the pathogenesis of sporadic PanNETs as well (see below).

MEN1 syndrome

Up to 100% of patients with MEN1 syndrome have PanNETs, which are usually multiple and occur in younger patients than sporadic PanNETs. While most PanNETs seen in MEN1 patients are nonfunctional, some are functional tumors.⁶ Of note, duodenal NETs are also very common in MEN1 patients, and most are gastrinomas. These small duodenal gastrinomas can metastasize to peripancreatic lymph nodes and mimic a pancreatic primary. The pancreas in MEN1 patients usually demonstrate numerous microadenomas and enlarged or architecturally abnormal islets (hyperplasia and dysplasia, respectively) in addition to the frank PanNETs. Loss of heterozygosity at 11q13 (containing the MEN1 gene) is always detected when islets transform into microadenomas in the MEN-1 patients.^{10,11}

VHL syndrome

PanNETs occur in 11–17% of VHL patients, with a median age of 37 years.¹² VHL-associated PanNETs are often small and multifocal, and they are almost always nonfunctional.¹³ VHL-associated PanNETs can have clear cell features, and there is a propensity for mixed serous–neuroendocrine tumors. In addition, VHL-associated PanNETs are associated with a better prognosis compared to sporadic PanNETs. Patients with the VHL syndrome usually do not have numerous microadenomas and abnormal islets, at least based on evaluation of routinely stained sections, but abnormal islets can be detected by immunohistochemistry based on aberrant expression of hypoxia-induced factor 1 α (HIF-1 α) and carbonic anhydrase IX.¹⁴

Table 1 – Incidence, hormone secretion, and clinical features of the four most common functional pancreatic neuroendocrine tumors.

	Incidence (million/year)	Association with MEN-1 (%)	Hormone	Syndrome	Clinical behavior
Insulinoma	1–3	5	Insulin	Whipple triad: neuroglycopenic symptoms, low blood sugar, and reversal of symptoms by glucose administration	Indolent (only 10% demonstrating an aggressive clinical course)
Gastrinoma	0.1	20	Gastrin	Zollinger–Ellison syndrome: complicated and uncomplicated ulcers and/or gastroesophageal reflux disease	Liver metastasis seen in 22–35% of cases at the initial diagnosis
VIPoma	0.05–0.2	6	VIP	large-volume secretory diarrhea, dehydration, and electrolyte disturbances	Aggressive clinical course seen in 50% of cases
Glucagonoma	0.01–0.1	20	Glucagon	Glucose intolerance, weight loss, and necrolytic migratory erythema	Aggressive clinical course in seen in >50% of cases

MEN-1, multiple endocrine neoplasia type 1; VIP, vasoactive intestinal polypeptide.

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