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Tips in Pancreatic Neuroendocrine Tumors (P-Nets)

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Abstract

A neuroendocrine tumor seems to arise from neural and endocrine cells. The most common are carcinoid rumors and neuroendocrine tumors of the pancreas (P-NETs). Most pancreatic tumors are sporadic but they also can arise from genetic syndrome such as MEN 1, MEN 2, VHL syndromes. They account for approximately 1% of pancreatic cancer in a range of age between 30-60 years. They can divide in Functional (F-PNETs) and non Functional tumors (NF-PNETs). Approximately 10% to 20% is functional. Functuctional P-NET may or may not have hormonal syndrome based on the hormone secretion: gastrin, insulin, glucagone, VIP, somatostatin. About 70% are insulinomas, 15% glucagonomas, 10% gastrinomas and somatostatinomas, which have a risk of metastases of 80% to 90%. Very rare is Vipomas, ACTHoma, GRFoma. Non functional PNET may have not any kind of symptoms and they are discovered in advanced stage. Appropriate diagnosis requires multidisciplinary team evaluating biochemical, radiological, endocrinological and surgical findings.

Pathogenesis

P-NETs have two probable origins of pancreatic NET: mature endocrine cells in the pancreas and multipotent stem cells. Ki-67 index, mitotic count and differentiation are the major components of P-NETs grading system (WHO) (Table 1) [1-4].

Biochemical, Clinical and Diagnostic Features

Insulinoma

It's the most common P-NET. Betha cells. Hormon secretion: Insulin. It's a benign type in almost 80%. Hepatic metastases inferior of 5%. Clinical symptoms: hypoglycemic symptoms, Whipple triad. Biochemical findings: Insulin level more than 3 mcLU/ml, C-peptide >0.6 ng/ml, pro-insulin >5 pmol/L. Dinamic tests: Calcium injection (Imamura test).

Gastrinoma

G cells. Hormone: gastrin. Associated with MEN 1 in 70% of cases. Malignant. 80% risk of distant metastases. Clinical symptoms: gastro-duodenal ulcers, dyspepsia, diarrhea (Zollinger-Ellison syndrome). Diagnosis: EGDS with biopsy. Biochemical: gastrin levels. A combination of fasting serum gastrin levels 10 times and gastric PH less 2 are diagnostic of gastrinoma. Dynamic tests: secretin stimulation.

Glucagonoma

Rare Malignant. 80% risk of metastase. Clinical signs: Recent-onset diabetes, cachexia, necrolytic erythematous skin rush. Biochemical findings: elevated glucagone in blood.

VIPoma

D1 cells. Hormone: VIP.Very rare. Malignant 40% to 70%. WHDA syndrome o Verner-Morrison syndrome. Clinical: watery diarrhea, Hypokaliemia, Dehydratation, Achlorhydria. Biochemical: elevated VIP.

Somatostatinoma

Rare D cells. Hormone: somatostatin. Malignancy 70%. Clinically: diabetes mellitus, cholelithiasis, diarrhea.

Diagnostic Evaluations

CT/MRI are the most common techniques for the diagnosis of pancreatic NET with a sensitivity and specificity >90%. CT/MRI can also be used for preoperative staging, follow-up and evaluation of treatment efficacy. EUS is a highly sensitive for small lesions with diameters from 0.3 cm to 0.5

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Table 1: WHO grading system.

Name	Cell type	Hormones secreted	Malignancy (%)	Pancreatic involvement (%)	Syndrome
Insulwoma	B	Insulin	10	99	Hypoglycemic symptoms, whipple triad
Gastrinoma	G	Gastrin	60-90	25	ZES (peptic ulcer, epigastric pain, diarrhea
VIPoma	D1	Vasoactive intestinal peptide	40-70	90	Watery diarrhea, hypokalemia, dehydration, achlorhydria
Glucagonoma	A	Glucagon	50-80	100	Rash, migratory erythema, diabetes mellitus, cachexia
Somatostatinoma	D	Somatostatin	70	55	Diabetesmellitus, cholelithiasis, and diarrhea
GRFoma	PP	Growth hormone-releasing hormone	60	30	Acromegaly
ACTHoma	NT	ACTH	95	16-Apr	Cushing's syndrome
Carcinoid	EC	Serotonin, tachykinins	60-88	1	Diarrhea, flushing, pain, asthma and heart disease

Table 2: Evaluate CgA, NSE, hormone features.

Items	Grade 1 (G1)	Grade 2 (G2)	Grade 3 (G3)
Ki-67 index	<3%	3-20%	>23%
Mitotic	<2/10 HPF	2-20/10 HPF	>20/10 HPF
Differentiation	Well differentiated	Well differentiated	Poorly differentiated

cm. Somatostatin Recptors Scanner (SRS) can detect tiny primary lesions and distant metastases.PET may be suitable for the detection of poorly differentiated tumors. The role of serum tumor markers in diagnosing pancreatic NET is limited Tumor markers: Chromoganin A (CgA), synaptophysin and/or neuron-specific enolase (NSE).

Treatment

Surgical resection is the only curative strategy for pancreatic NET. 6 Furthermore, cytoreductive surgery can control the secretion of activated hormones and improve the survival for patients with advanced pancreatic NET and can be an optional strategy for physically fit patients with metastatic, well-differentiated pancreatic NET with an overall survival (OS) of 60 months versus 30 months in non cytoreductive or not fit patients. Somatostatin analogues or CHT are the first or second line approach in advanced diseases.

Conclusion

Pancreatic NET are a group with high heterogeneity and a better prognosis than exocrine pancreatic cancer. The incidence of pNETs is increasing and the majority of pNETs are nonfunctional. The prognosis worsens in patients with metastatic tumors or poorly differentiated pancreatic NET. Surgical treatment is the first choice treatment. Somatostatin analogue or cytotoxic CHT are the alternative. The efficacy of sunitinib and everolimus support the role of targeted agents as a new option in the first- or second-line treatment of pancreatic NET.

Summary

Evaluate CgA, NSE, hormone features (Table 2), symptoms and signs, radiologic findings (CT, MRI, SRS, PET, EUS), decide after a multidisciplinary team planning, analyze histopathological findings (Ki-67, mitotic count, differentiation).

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