Pancreatic Neuroendocrine Tumors - NET

Clinical Background

Pancreatic neuroendocrine tumors (PNET) are rare tumors of pancreatic neuroendocrine cells that may be functional or nonfunctional.

Epidemiology

- Incidence – 1-1.5/100,000
- Age – onset 40s-50s
- Sex – M:F, equal
- Occurrence – usually sporadic

Risk Factors

- Genetic – May be associated with multiple endocrine neoplasia type 1 (MEN 1), von Hippel-Lindau syndrome, and type 1 (peripheral) neurofibromatosis

Pathophysiology

- Solid or cystic tumors located anywhere within the pancreas
- Tumors may be functional or non-functional
  - Functional tumors secrete hormones to produce classic clinical syndrome (eg, Verner-Morrison syndrome associated with vasoactive intestinal polypeptide [VIP] secretion)
  - Non-functional tumors may secrete hormones but do not cause symptoms
- Frequency of occurrence – non-functional >insulinoma >gastrinoma >glucagonoma >VIPoma >somatostatinoma
- Molecular pathogenesis of pancreatic NETs is incompletely understood
  - Loss of heterozygosity at 11q13 and *MEN1* mutations have been identified in sporadic NETs

Clinical Presentation

- Tumor increasingly identified incidentally by imaging
- Patients may present with one of five common hormonal syndromes
  - Insulinoma
  - Zollinger-Ellison syndrome
  - Glucagonoma
  - Verner-Morrison syndrome
  - Somatostatinoma syndrome

Treatment

- Relief of symptoms caused by hormone secretion
- Surgical resection
- Somatostatin analogues

Diagnosis

- Indications for testing – pancreatic mass; presentation of one of the five functional syndromes associated with the tumor
- Laboratory testing
  - Elevated levels of insulin, C-peptide, gastrin, glucagon, VIP, or somatostatin
  - Chromogranin A (sensitivity 60-100% in metastatic disease, 50% in early disease)
- Histology

- Nested or trabecular arrangement of small- to medium-sized cells
  - Finely granular eosinophilic cytoplasm
  - Central, round to oval nuclei
  - Stippled chromatin ("salt and pepper")
- Immunohistochemistry – chromogranin and synaptophysis
  - May also stain for commonly secreted hormones
    - Positive staining is not always associated with clinical syndrome
    - Not sufficient as diagnosis without clinical syndrome
- Imaging Studies
  - CT
  - MRI
  - Somatostatin-receptor scintigraphy (not useful in insulinomas)

Prognosis

- Malignancy determined by tumor cell invasion of surrounding structures
  - Duodenum, bile duct, lymph nodes, or peripancreatic fat may be involved
  - Each pancreatic NET variant has a different risk of malignant behavior
- Tumors may be categorized according to WHO or TNM classification
- Survival rate is excellent for patients with complete resections (90-100%), but is lower for those with metastatic disease (25-50%)

Differential Diagnosis

- Solid-pseudopapillary tumor
- Acinar cell carcinoma
- Pancreatoblastoma
- Paraganglioma
- Pancreatic ductal adenocarcinoma
- Chronic pancreatitis

Lab Tests

Indications for Laboratory Testing

Tests generally appear in the order most useful for common clinical situations. For test-specific information, refer to the test number in the ARUP Laboratory Test Directory on the ARUP Web site at www.aruplab.com.

Test Name and Number	Recommended Use	Limitations	Follow Up
Chromogranin A 0080469 Method: Enzyme Immunoassay	Monitor pancreatic neuroendocrine tumors	Nonspecific tumor marker in diagnosis May be elevated due to proton pump inhibitor therapy or impaired renal function Results obtained with different assay methods or kits cannot be used interchangeably	

Gastrin 0070075 Method: Chemiluminescent Immunoassay	Diagnose Zollinger-Ellison syndrome Patient should be fasting		
Glucagon 0099165 Method: Radioimmunoassay	Diagnose glucagonoma		
Glucose, Plasma or Serum 0020024 Method: Enzymatic	Measure blood sugar levels		
Insulin, Fasting 0070063 Method: Chemiluminescent Immunoassay	Measure insulin levels		
Proinsulin/Insulin Ratio 0070256 Method: Refer to individual components	Measure insulin/proinsulin levels and ratio		
C-Peptide, Serum or Plasma 0070103 Method: Chemiluminescent Immunoassay	Measure C-peptide		
Somatostatin 0098192 Method: Extraction/ Radioimmunoassay	Diagnose somatostatinoma		
Vasoactive Intestinal Peptide 0099435 Method: Radioimmunoassay	Measure vasoactive intestinal peptide to determine likelihood of cancer		

Immunohistochemistry Stain Offering arup005 Method: Immunohistochemistry	For fixed tissue samples, consultative services as well as immunohistochemical staining for synaptophysin, chromogranin, NSE, AE1/AE3, PGP 9.5, gastrin, glucagon, insulin, and somatostatin are available		

Additional Tests Available

Test Name and Number	Comments
Pancreatic Polypeptide 0099436 Method: Radioimmunoassay	

General References

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Tumor Markers

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Zollinger-Ellison Syndrome - Gastrinoma

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