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GI Neuroendocrine Tumors

Neuroendocrine tumors

"Neuro"→ contain <u>secretory granules</u> (like synaptic vesicles)
"Endocrine"→ <u>secrete</u> peptides and amines locally

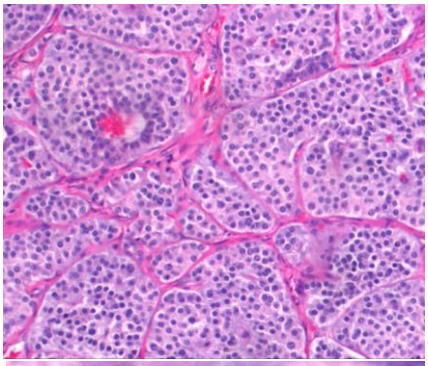
Tumors can arise anywhere in the GI tract. They have characteristic morphology and protein expression.

<u>Immunohistochemical markers:</u> *(Note, these may also recognize neurons and neuroblastic cells)*
Synaptophysin and **Chromogranin**→ recognize the dense core granules
CD56 and Neural-Specific Enolase (**NSE**) → Less specific
Often "dot-like" perinuclear staining with cytokeratin; **INSM1**→ New NE transcription factor (nuclear stain)

Well-Differentiated Neuroendocrine Tumors

aka "carcinoid"

<u>Morphology</u>: Uniform, **round nuclei**
"Salt and Pepper" fine, speckled chromatin
Granular cytoplasm
Organoid architecture (i.e., nested, cords, glands-like rosettes, or ribbons)
No necrosis. Variable stroma. Can see amyloid deposition.

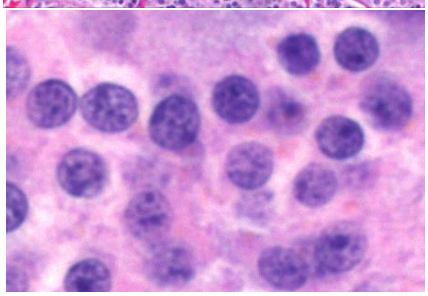


<u>Molecular</u>: MEN1, DAXX, ATRX mutations common (particularly in the pancreas)

Malignant, **but slow-growing, indolent** progression.
Early NETs have a low risk of metastasis

Somatostatin receptors→ can detect with "DOTA" PET radiographically

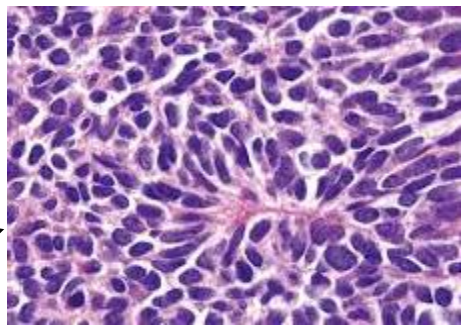
Graded 1-3 based on Ki67/Mitoses (see next page)



Poorly-Differentiated Neuroendocrine Carcinomas

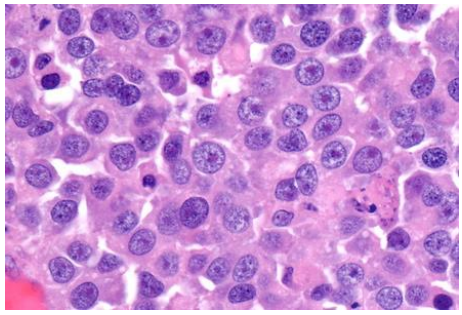
Often arise from non-neuroendocrine tumors (and subsequently *<u>develop</u>* neuroendocrine differentiation.
Sheet-like growth
Not Graded
Malignant! Very metabolically active/**rapidly growing**
→ see on normal FDG-PET scan

<u>Molecular</u>: p53, RB1 (and other carcinoma-associated mutations)
<u>Treatment</u>: Platinum-containing chemotherapy



Small Cell Neuroendocrine Carcinoma

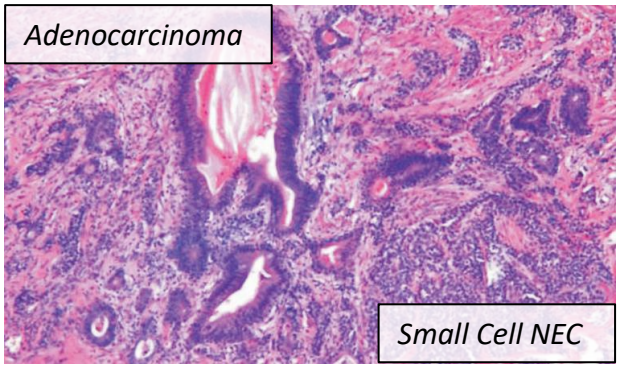
<u>Morphology</u>: Fusiform nuclei, **finely granular chromatin**, **scant cytoplasm**, and nuclear molding. Extensive necrosis.
Tons of mitoses. Ki67 almost 100%.



Large Cell Neuroendocrine Carcinoma

<u>Morphology</u>: Large, round nuclei, with **prominent nucleoli**, and moderate amounts of cytoplasm. Sheet-like to nested growth.
Ki67 often in 60-80% range

Mixed Neuroendocrine-Non-neuroendocrine Neoplasms (MiNEN)



A neuroendocrine tumor or carcinoma **with a non-neuroendocrine component** (both >30% of tumor)

Can be adenocarcinoma, squamous cell carcinoma, etc..

Presumed to be **clonally related**
(A non-neuroendocrine carcinoma dedifferentiates/transdifferentiates to a NEC)

Common sites

Most Neuroendocrine Tumors are well-differentiated. NETs are overall relatively rare.
In GI tract, they are often polypoid and centered in the submucosa or muscle with intact overlying mucosa.

Small intestine—most common site, often in ileum. Tend to present later, with advanced disease (either liver metastases, or large lymph node metastases at root of mesentery).
Appendix—often small and incidental.
Rectum
Stomach—three distinct setting/types *(see separate stomach tumor guide)*

Pancreas—arise in the pancreatic parenchyma (from islets) and grow into the peripancreatic fat, or, less commonly, into the pancreatic duct.

Site of Origin

NET metastasis with unknown primary? We can do a panel of stains to try to locate the primary. Also, the clinician can do a DOTA-PET

CDX2→ Small intestine **TTF1**→ Lung **IL1**→ Pancreas/Rectum **SATB2**→ Rectum

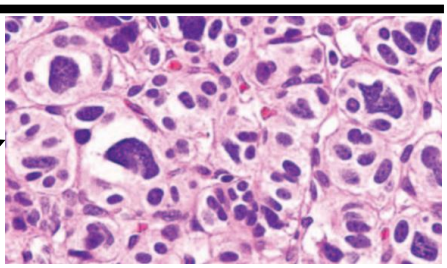
Grading

Classification/Grade	Ki67 Proliferation Index	Mitotic index
Well-differentiated		
Grade 1	<3%	<2
Grade 2	3-20%	2-20
Grade 3	>20%	>20
Poorly-differentiated		
Small cell type	>20%	>20
Large Cell type		

Ki67 Proliferation index based on evaluation of ≥ 500 cells in a "hot spot."

Mitotic count based on evaluating 50 Hpfs, but reported per 10 Hpfs.

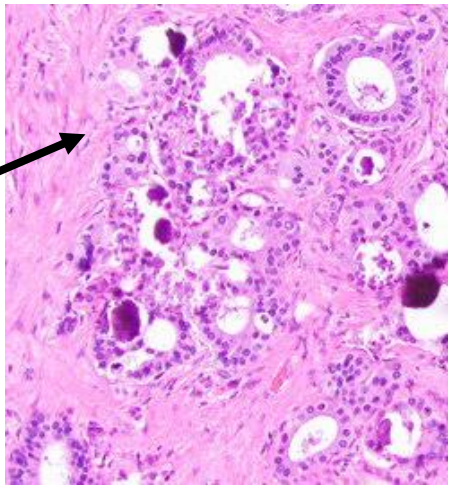
Noteworthy Variants



Cystic: although most NET's are solid, some, particularly in the pancreas, can undergo central cystic degeneration

Pleomorphic nuclei: "endocrine atypia" seen in endocrine organs can be seen in WD-NET. These changes appear to be degenerative, are not associated with a higher Ki67, and have no prognostic importance.

Oncocytic: abundant granular oncocytic cytoplasm with eccentric nuclei, appearing rhabdoid. Can have pleomorphic nuclei to.



Somatostatinoma: often ampullary with a glandular appearance and psammomatous calcifications. Can be mistaken for an adenocarcinoma.

Clear cytoplasm: associated with Von Hippel Lindau

Lipid-rich: lots of small lipid vacuoles

"**Adenoma-Carcinoid:"** Rarely, small neuroendocrine clusters are found incidentally next to an adenoma in a polypectomy. The NE proliferation is typically small, and is possibly reactive to the "tumor milieu."

Tumor Syndromes

"Functioning"→ hormone secreting → characteristic syndrome

Functioning tumors are often **pancreatic** and **discovered sooner** due to symptoms.
Non-functioning tumors are often discovered later (with metastases) or incidentally.

Insulinoma→ Usu. Small, present early with hypoglycemia

Gastrinoma→ Zollinger-Ellison Syndrome → acid hypersecretion → extensive peptic ulcers
Associated with MEN1, most commonly tumor in proximal duodenum

VIPoma→ Watery diarrhea with hypokalemia and achlorhydria

Glucagonoma→ Necrolytic migratory erythema, diabetes, stomatitis

Somatostatin → diabetes, cholelithiasis, diarrhea → can have glandular growth and psammoma bodies

"Carcinoid syndrome"→ Serotonin and Kallikrein secretion → Flushing, diarrhea, bronchoconstriction.
Usu. Only if liver metastases. Elevated serum 5-HT and/or urine 5-HIAA

Family Syndromes

MEN 1: Majority develop NETs (Pancreas > stomach/duodenal). Often multifocal proliferation of islets, with microadenomas (<0.5 cm, non-functional) and WD-NET's (>0.5 cm or functional). Also, Pituitary adenoma, parathyroid hyperplasia, bronchial and thymic NETs.

Neurofibromatosis 1: Increased risk of WD-NET (in addition to lots of tumors, like neurofibromas, MPNST's, GISTs, etc…), particularly ampullary somatostatinomas.

Von Hippel Lindau: Can have WD-NET's with clear cells. Also, hemangioblastomas, clear cell renal cell carcinomas, and adrenal tumors.

Tuberous Sclerosis: Pancreatic insulin and somatostatin-producing NET. Also, angiomyolipomas and other hamartomas