Last updated: 8/26/2024

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GI Neuroendocrine Tumors

Neuroendocrine (NE) tumors

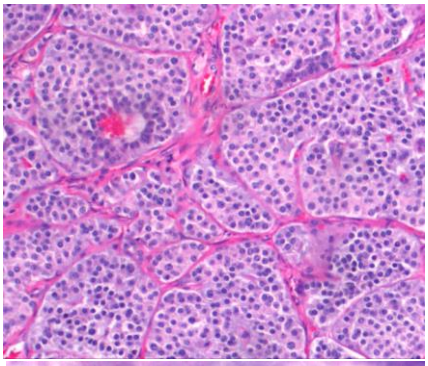
"Neuro"→ contain <u>secretory granules</u> (like synaptic vesicles)
"Endocrine"→ <u>secrete</u> peptides and amines locally

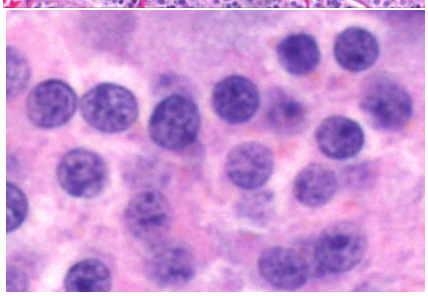
Tumors can arise anywhere in the GI tract. They have characteristic morphology and protein expression.

<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

WD-NET
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)

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

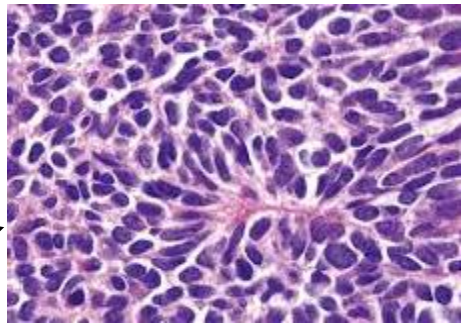
Somatostatin receptors→ can detect with "DOTA" PET radiographically

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

Poorly-Differentiated Neuroendocrine Carcinomas (NEC)

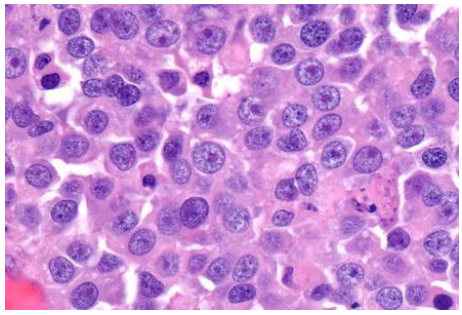
Often arise from *<u>non</u>*-neuroendocrine tumors (and subsequently *<u>develop</u>* neuroendocrine differentiation.
Sheet-like growth
Not Graded
Malignant! Very metabolically active/**rapidly growing**
→ see on normal FDG-PET scan

<u>Molecular</u>: p53, RB1 (and carcinoma-associated mutations like KRAS)
<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 very high; often 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

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.

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, with a good prognosis.
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.

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

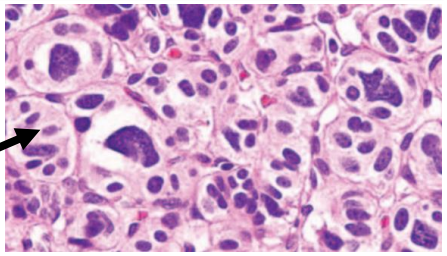
Glucagonoma→ Necrolytic migratory erythema, diabetes, stomatitis

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

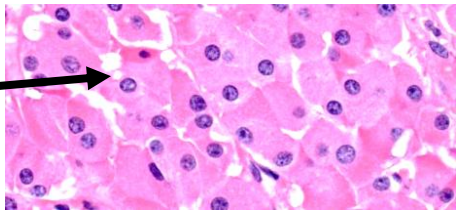
Noteworthy Variants

Mostly noteworthy as they can mimic other Dxs!



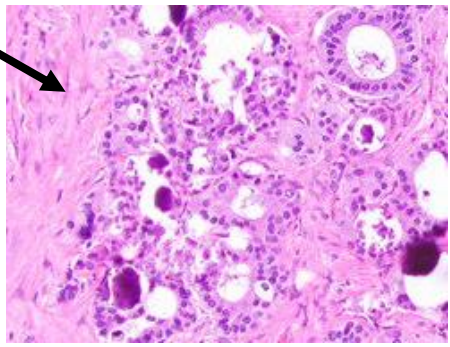
Cystic: although most NET's are solid, some, particularly in the pancreas, can undergo central cystic degeneration.

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. More aggressive. Easy to confuse with HCC.

Somatostatinoma: ("Glandular Duodental NET") often ampullary with a glandular appearance and psammomatous calcifications. Can be mistaken for an adenocarcinoma. Extra IHC (+) S100, mCEA highlights secretions in glands



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."

Bottom line, NET's can look like lots of things, so keep in your DDX whenever things don't look quite normal or look "weird" in the GI tract!

For more discussion of GI NET tumor variants, check out this article by Xue et al: PMID: 32488621

Family Syndromes

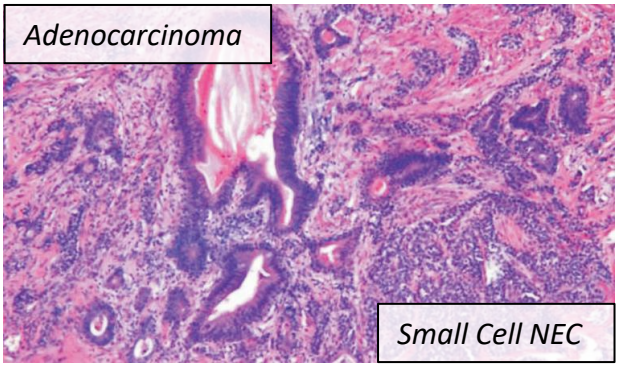
MEN 1: Majority develop NETs (Pancreas > stomach/duodenal). Often multifocal proliferation of islets, with microadenomas (<0.5 cm, non-functional) and WD-NET's (>0.5 cm or functional). Also, Pituitary adenoma, parathyroid hyperplasia, bronchial and thymic NETs.

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

Mixed Neuroendocrine-Non-neuroendocrine Neoplasms (MiNEN)



A neuroendocrine tumor or carcinoma **with a <u>non</u>-neuroendocrine component** (both >30% of tumor), which can be adenocarcinoma, squamous cell carcinoma, etc..

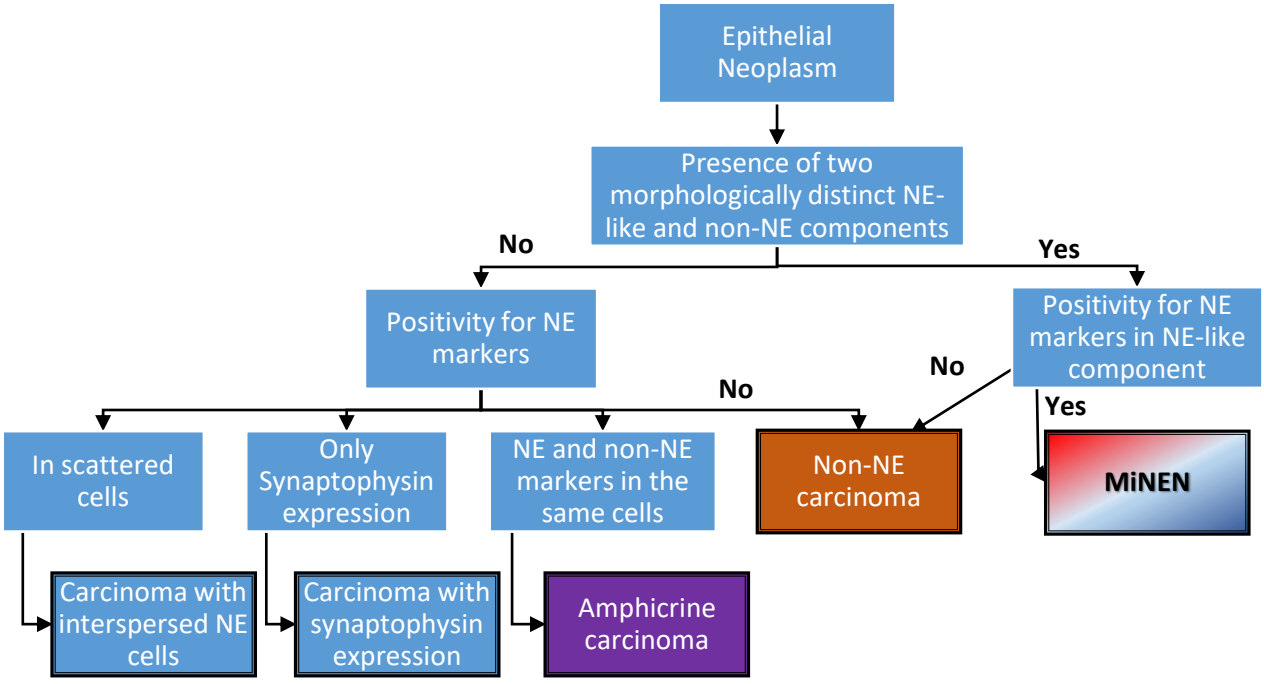
<u>Distinct</u>, <u>separate</u> cellular components.

<u>Conceptual category</u>, **<u>not</u>** a diagnosis→ diagnose/state separate components (e.g., "*Mixed adenocarcinoma – small cell carcinoma*")

Instead, use the term "**<u>Amphicrine</u>**" if it's the *<u>same</u>* cells that exhibit both NE and non-NE morphology and staining.

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

<u>An Algorithmic Approach to Classifying Mixed Neoplasms</u>



Modified from: Rindi G, et al. Overview of the 2022 WHO Classification of Neuroendocrine Neoplasms. Endocr Pathol. 2022 Mar;33(1):115-154 PMID: 35294740.

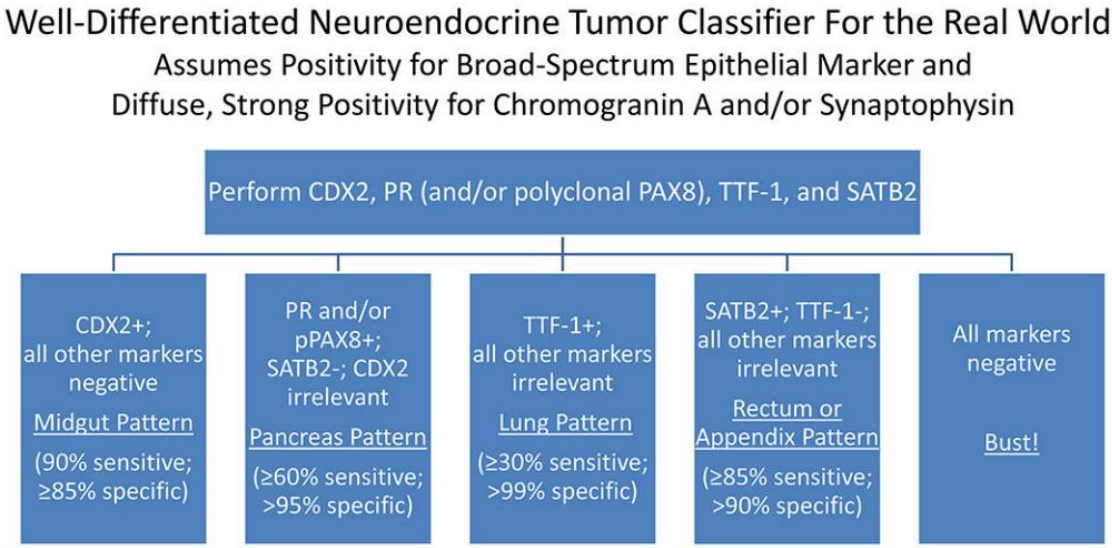
"Bellizzi Algorithms"

I strongly recommend checking out Dr. Andrew Bellizzi's articles detailing how to use IHC to address some of our frequent NE tumor problems.

Bellizzi AM. Hum Pathol. 2020 Feb;96:8-33. PMID: 31857137.
Bellizzi AM. Adv Anat Pathol. 2020 May;27(3):114-163. PMID: 32205473

1) Where did this NET (liver) metastasis come from?

Try the algorithm below.
Also, the clinician can do a DOTA-PET



2) Is this tumor a NE tumor or carcinoma?

Try the algorithm below.
Also, the clinician can do a DOTA-PET (positive in NET) and normal PET (positive in NEC), usually….