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Rare and Genetic Disease Network

CME

Neuroendocrine Tumors (NETs) Abstract

Highlights from ENDO 2020

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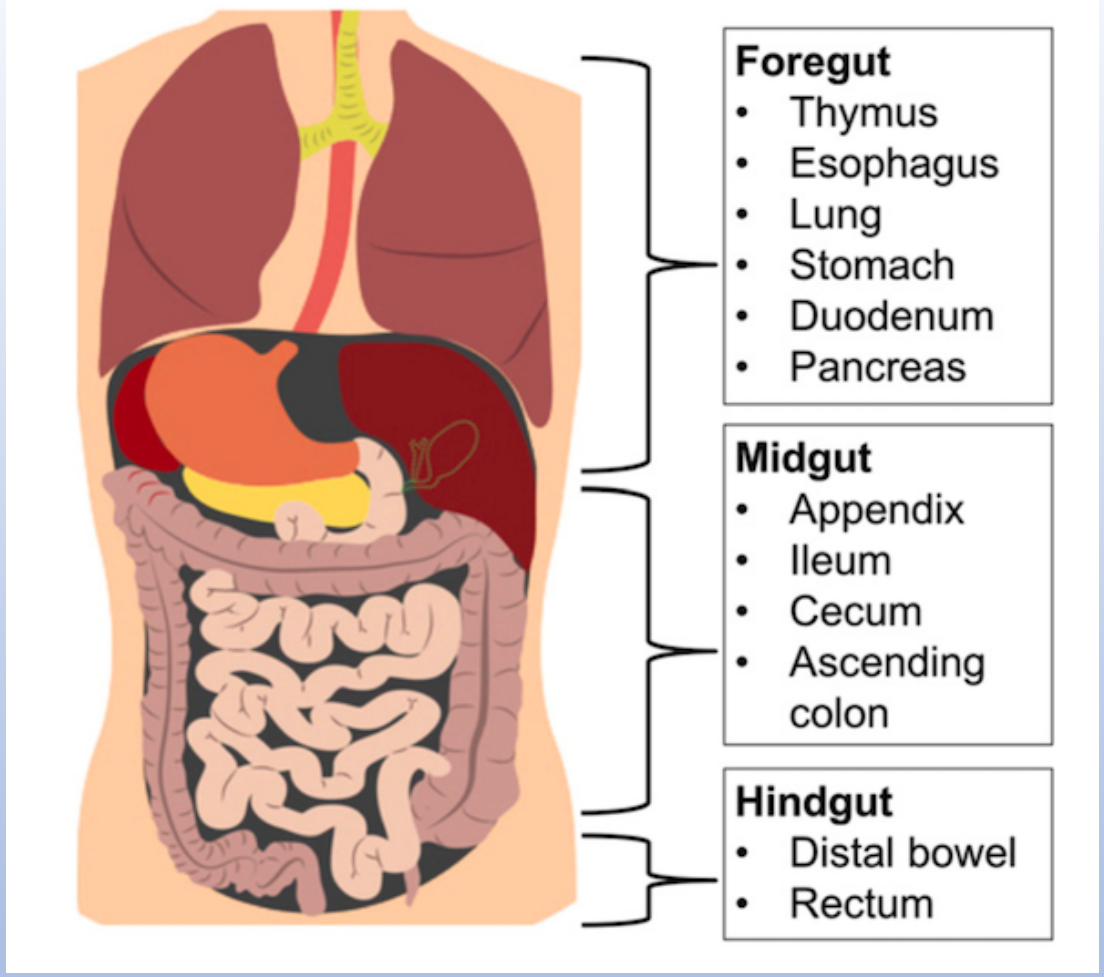
What are NETs?

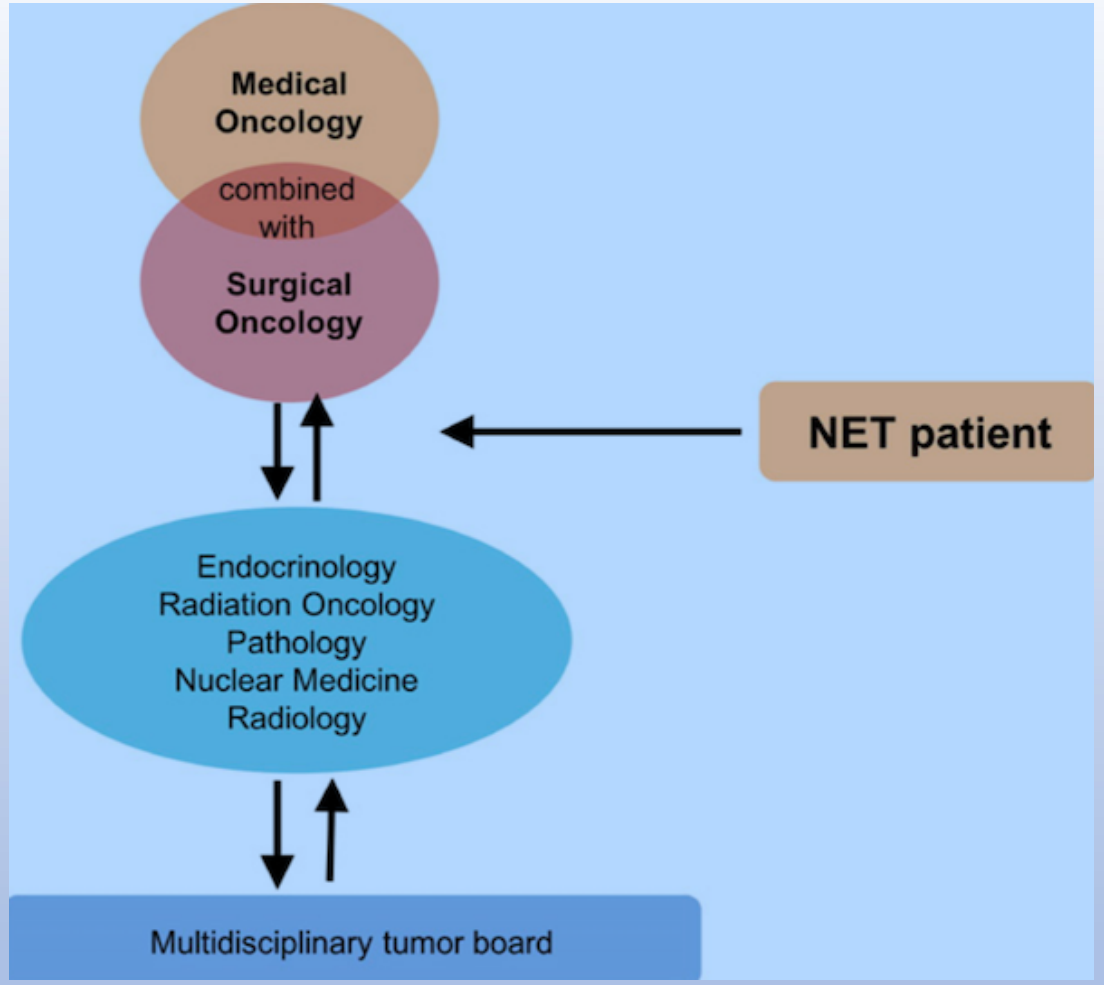
- Tumors that can lead a variety of symptoms
- 125,000 people current living with carcinoid or NETs in the U.S.
- Often difficult to diagnose and treat.
- Many examples of complex nature of Nets will be presented here



What is NETs? Mount Sinai Hospital https://www.mountsinai.org/care/gastroenterology/services/neuroendocrine-carcinoid-tumors

Managing NETs?

- Team approach to care
  - Oncologists
  - Radiologists
  - Pathologists
  - Family Practice
  - Gastroenterologists
  - Endocrinologists
  - Pulmonologists/Thoracic surgeons
  - Cardiologists/Cardiac surgeons



What is ENDO 2020?

ENDO Annual Meeting

- Scheduled for March 28-31, 2020 in San Francisco, CA
- Live event cancelled due to COVID-19
- However, abstracts published in *Journal of the Endocrine Society*

Cushing Syndrome from NET

Nektaria Papadopoulou-Marketou et al. Periodic Cushing syndrome in a patient with an intestinal neuroendocrine tumor (NET). A novel case report

- 53-year old male is the first case of ectopic Cushing disease caused by intestinal NET.
- Differential diagnosis between pituitary and ectopic Cushing disease due to ACTH or CRH hypersecretion is complicated
- Surgical removal of neoplasm in small bowel region allowed person to return to normal
- Authors conclude that in patients with Cushing symptoms but no visible pituitary lesions on MRI, further investigation for ectopic ACTH-driven Cushing syndrome is suggested

Jian Zhang et al. Ectopic Cushing syndrome due to metastatic neuroendocrine tumor to the breast

- 38-yr old female presented with ACTH-dependent Cusing syndrome. Pituitary MRI normal
- DOTATATE scan showed 0.8 cm area uptake in right breast and mediastinal lymphademopathy
- Chemotherapy and lumpectomy preformed but Cushing symptoms worsened. Chemotherapy halted and follow-up scans showed uptake in mediastinal lymph nodes
- Bilateral adrenalectomy performed plus 10 cycles of chemotherapy. Patient doing well

Papadopoulou-Marketou NS et al. *J Endo Soc.* 2020; 4 (suppl): SAT-142. Zhang Jet al. *J Endo Soc.* 2020; 4 (suppl): SUN-927.

New Treatment Option for Cushing's Syndrome

Elena Thampy Cherian et al. Etomidate – an under utilized but safe and efficacious drug to treat acute severe Cushing's syndrome-case reports of ectopic ACTH syndrome from neuroendocrine malignancies

- Low dose, non-hypnotic, etomidate rapidly lowers cortisol. Is it an under utilized drug due to concerns about sedation and ICU monitoring?

Case 1

- 44-yr old woman the HTN, diabetes, recently diagnosed pancreatic NET with liver metastases
- Elevated cortisol and ACTH
- Developed worsening psychosis (likely due to hypercortisolism)
- Given etomidate (2.5 mg/hr and titrated up)
  - Rapid drop in cortisol levels and improvement in mentation
  - Later weaned off etolmidate and eventually underwent a successful bilateral adrenalectomy

Case 2

- 51-yr old man with one month of hematochezia presented with hypertension, sever hypokalemia, metabolic alkosis, and QTc prolongation. Cortisol and ACTH elevated.
- Imaging showed pancreatic mass and multiple hypodense liver lesions. Biopsy confirmed metastatic NET.
- Chemotherapy, ketoconazole, and metyrapone failed to lower cortisol
- Etomidate drip started (3 mg/hr), resulting in rapid drop in cortisol levels
- Attempts to wean off etomidate were unsuccessful and patient eventually underwent bilateral adrenalectomy.

Pahsa P et al. *J Endo Soc.* 2020; 4 (suppl): SAT-LB303.

Psychiatric Symptoms from Co-secretion of Multiple Hormones by NET

Siti Sanaa Wan Azman et al. Debilitating neuropsychiatry symptoms in pancreatic insulinoma co-secreting serotonin and IGF-1

- 68-yr old female presented with recurrent diaphoresis, palpitations, tremors, chest tightness
  - Symptoms associated with episodic paroxysms of flushing and diarrhea
  - Physical examination unremarkable
- Most blood chemistry within normal range except for:
  - Insulin medicated hypoglycemia observed blood sugar; 2.5 mmol/l
  - Urine 5-HIAA elevated; 2430.37 umol/day
  - IGF-1 elevated; 416 ug/L
- 2 months later, patient presents with delirium, incoherience, agitation, restlessness. Required a full time caregiver to assist her
- Focus on the pancreas
  - Gallium-68 PET CT; endoscopic ultrasound; ASVS
  - Lesion at the head of the pancreas
- Authors speculate debilitating neuropsychiatric symptoms due to pancreatic NET that secretes serotonin, insulin, and IGF-1

Wan Azman SS et al. *J Endo Soc.* 2020; 4 (suppl): MON-911.

Venous thromboembolic events in MEN1

Maya E Lee et al. Are venous thromboembolic events increased in MEN1 patients?

- Natural history study involving 287 patients with MEN1 mutations between 1991 - 2019
- Total of 34 had VTE (13.4%)
  - Approx 2-fold higher than general population

K-M analysis	Non-VTE	VTE	*P* value
Survival	81.1 + 2.23 yrs	77.4 + 3.45 yrs	0.96 (NS)

- Of the patitents with VTE
  - 80% had hyperparathyroidsism
  - 21% had hyperprolactimemia
  - 62.5% had hypergastrinemia
  - 84.6% had pancreatic NETs

Lee ME et al. *J Endo Soc.* 2020; 4 (suppl): SUN-124.

Acromegaly from Bronchial NET

Jasmine Bahrami et al. A Case of Acromegaly Secondary to Ectopic Growth Hormone-Releasing Hormone (GHRH) Secretion from a Bronchial Neuroendocrine Tumour

- Case Study
  - 42-yr-old female initially suspected of having small cell lung cancer and treated with chemoradiotherapy
  - Also showed signs of acromegaly (Increased digital girth, weight gain, enlarged tongue) but showed completely normal pitituary)
  - Subsequent tests showed elevated GHRH (73 pg/ml; normal range 5 – 18 pg/ml)
  - Biospy revealed ACTH producing pulmonary NET (not small cell lung cancer)
  - Treatment
    - Sandostatin
    - Left pneumonetomy
  - Treatment successful

Bahrami J et al. *J Endo Soc.* 2020; 4 (suppl): SUN-930.

Glucagonoma Presenting with Skin Rash

Siroj Dejhansathit et al. Undiagnosed chronic eczema as a presentation of glucagonoma in MEN1 syndrome

- Case Study
  - 51-yr-old male with type 2 DM and hypertension presented to clinic multiple times with rash on legs and genital area
  - Topical steroids not affective. When skin lesions healed, new ones appeared
  - Rash spread to tunk and face. Weight loss and stomatitis also occurred
  - CT/scintigraphy revealed mass at the pancreatic tail and multiple modules in liver
  - Serum glucagon = 923 pg/ml
  - Treatment – surgical removal of tumors
  - Treatment successful
  - Lesson: Glucoagonomas are rare pancreatic tumors difficult to recognize but often associated with necrolytic migratory erythema

Dejhansathit S et al. *J Endo Soc.* 2020; 4 (suppl): MON-912.

Somatostatin Analogs: Nurses' Preference

- Somatostatin agonists used to treat carcinoid syndrome

Daphne Adelman et al. et al. An international simulated use study (PRESTO) to evaluate nurse preferences between the lanreotide autogel new syringe and octreotide long-acting release syringe

- PRESTO Study
  - 90 nurses invited to compare lanreotide autogel/depot syringe and octreotide long-acting release syringe
  - 97.8% expressed preference for lanreotide autogel/depot syringe
    - 85.6% strong preference; 12.2 slight preference
  - Key attributes were 'fast administration' and 'confident syringe would not clog'
  - Shorter needle may also be a factor

Adelman DT et al. *J Endo Soc.* 2020; 4 (suppl): MON-LB47.

Update of HSA I-131-MIBG in Metastatic Pheochromocytomas/paragangliomas

- Pheochromocytomas/paragangliomas PPGLs are rare NETs that often secrete catecholamines leading to hypertension, arrhythmias, headaches etc.
- 5 year survival rate as low as 12%
- High-specific-activity I-131 meta-iodobenzylguanidine [HSA I-131-MIBG] approved to treat pheochromocytoma/paraganglioma (PPGL) that are positive for NE transporter
- FDA approval in 2018 largely based on StudyIB12B, a multicenter, open-label, Phase 2 study
- Study published in 2019 (Pryma et al) based on 12 month data showing the radiotherapy to be safe and effective with 92% of patients showing a partial response or stable disease
- Jimenez et al published updated data from that ongoing study for ENDO 2020

Pryma DA et al J Nucl Med 2019;60:623-630.

Update of HSA I-131-MIBG in Metastatic Pheochromocytomas/paragangliomas

Camilo Jimenez et al. A multi-center, open-label, pivotal Phase 2 study of Azedra (HSA I-131-MIBG) in patients with unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma: updated long-term survival and safety

- 74 patients with advanced PPGL given HAS I-131-MIBG

	One therapeutic dose (n=68)	Two therapeutics doses (n=50)
Clinical benefit observed	71.4%	98%
Median survival time	19.3 months	49.1 months

- Overall survival 73.8% at 2 yrs, 47.5% at 4 yrs, and 41.5% at 5 yrs
- AEs: nausea, fatigue, myelosuppression
- Late radiation toxicity included 7 patients with secondary malignancies (MDS, AML, ALL, colon cancer, lung cancer). MDS, AML, and ALL were suspected of being linked to I-131 therapy.

Temozolomide active in Metastatic Pheochromocytoma/paragangliomas (PPGLs)

Tobias Skrebsky de Almeida et al. Successful response of temozolomide (TMZ) in two patients with metastatic pheochromocytoma/paragangliomas (PPGLs)

Case 1

- 14-yr old female with retroperitoneal lesion close to celiac trunk, superior mesenteric artery, renal arteries, aorta, left renal vein and vertebral bodies of T10, T11 and T12
- Chest CT showed lung metastases
- 11 months later, primary abdominal lesion and lung metastases increased
- Temozolomide started and after 11 cycles, lesions decreased in size 30% with no progressive lesions.

Case 2

- 31-yr old female underwent right adrenalectomy and nephrectomy for pheochromocytoma
- 7 years later, lesions in liver and lung observed
- Sorafenib used for 7 months.
- 3 years later, underwent surgery to remove lesion in right lung. Refused further surgery for left lung lesion.
- 1 year later, left lung lesion increased and and mediastinal and paratracheal lymphadenomegaly developed
- Temozolomide started, and after 7 cycles, a chest CT showed complete regression of lung and lymph node metastases

De Almeida TS et al. *J Endo Soc.* 2020; 4 (suppl): SUN-932.

Summary

- NETS are a group of rare and diverse group of tumors
- Multiple hormonal syndromes can be difficult to diagnose and treat.
- New data at ENDO 2020 highlight:
  - Diagnosis of rare hormonal syndromes
  - Novel therapies are showing promise
  - Rigorous clinical trials are needed to optimize treatment of these rare diseases.