A, B ... Zs
of
Neuroendocrine Tumours (NETs)

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Objectives

- What is the neuroendocrine system
- Where can neuroendocrine cancers start
- General statistics
- Diagnosis:
  - Pathology, Biomarker tests, Imaging
- Classification
Disclosures

• Thanks to Dr. Celia Marginean, Dr. Maroun and others use of slides
What is the Neuroendocrine System?
Neuroendocrine cells

- Neuroendocrine system made up of neuroendocrine cells
- Special group of nerve cells that can also produce hormones that influence body functioning
Examples of Neuroendocrine system
Where can neuroendocrine tumours start?

Variety of the spice of Life
Where can neuroendocrine tumours start?
NE cells are widely distributed throughout the epithelia of the stomach, intestines, distal esophagus, and anus.

At least 14 types of NE cells populate the GI mucosa.

### General Organization of the NE Gastrointestinal System

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Localisation</th>
<th>Products</th>
<th>Factors that regulate secretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>Gastrointestinal tract</td>
<td>Somatostatin</td>
<td>Hormones, neural factors, and acid</td>
</tr>
<tr>
<td>Enterochromaffin (Kulchitsky cells) (and lung)</td>
<td>Gastrointestinal tract</td>
<td>Serotonin, substance P, guanylin, and melatonin</td>
<td>Luminal factors, hormones, and neural factors</td>
</tr>
<tr>
<td>Enterochromaffin-like</td>
<td>Stomach</td>
<td>Histamine</td>
<td>Hormones, gastrin, and neural factors</td>
</tr>
<tr>
<td>G</td>
<td>Stomach and duodenum</td>
<td>Gastrin</td>
<td>Amino acids, neural factors, and acid</td>
</tr>
<tr>
<td>Gr</td>
<td>Gastrointestinal tract</td>
<td>Ghrelin</td>
<td>Luminal factors and hormones</td>
</tr>
<tr>
<td>I</td>
<td>Duodenum</td>
<td>Cholecystokinin, gastrin, etc</td>
<td>Lipids and neural factors</td>
</tr>
<tr>
<td>K</td>
<td>Duodenum and jejumun</td>
<td>Gastric inhibitory polypeptide</td>
<td>Nutrients and hormones</td>
</tr>
<tr>
<td>L</td>
<td>Small intestine</td>
<td>Glucagon-like peptide, peptide YY, and neuropeptide Y</td>
<td>Glucose and hormones</td>
</tr>
<tr>
<td>Motilin</td>
<td>Duodenum</td>
<td>Motilin</td>
<td>Neural factors and luminal factors</td>
</tr>
<tr>
<td>N</td>
<td>Small intestine</td>
<td>Neurotensin</td>
<td>Lipids</td>
</tr>
<tr>
<td>S</td>
<td>Duodenum</td>
<td>Secretin</td>
<td>Acid</td>
</tr>
<tr>
<td>VIP</td>
<td>Gastrointestinal tract</td>
<td>Vasoactive intestinal peptide</td>
<td>Neural</td>
</tr>
<tr>
<td>X</td>
<td>Stomach</td>
<td>Amylin</td>
<td>Not defined</td>
</tr>
</tbody>
</table>
Statistics
Statistics

• 0.5% of all cancers
  • Breast cancer 25% all cancer
• 2.5 to 5 cases per 100,000
  • Breast cancer 100 per 100,000
• Ottawa (1.5 million) = 75 new cases/year
• Toronto (3 million) = 150 new cases/year
QUESTION

- The number of new neuroendocrine tumour are currently....
  - Rising
  - Decreasing
  - Stable
QUESTION

- The number of new neuroendocrine tumour are currently….
  - Rising
  - Decreasing
  - Stable
NET Incidence Is Increasing

US SEER data show a 5-fold increase in the past 30 years

SEER = Surveillance, Epidemiology and End Results.
Increasing Incidence of NETs: Ontario


Age-adjusted rates standardized to 1991 in rate per 1 million population by year of diagnosis.

NETs Are the Second Most Prevalent Type of GI Malignancy

2x more prevalent than pancreatic cancer

Prevalence in SEER Database
Neuroendocrine tumours: Origin

- **Bronchopulmonary system**: 28%
- **Digestive system**: 64%
- **Other**: 8%

**Site**

- **Other**: 2.3
- **Colon and rectum**: 28
- **Small intestine**: 28.5
- **Stomach**: 4.6

- **Colon, except appendix**: 9
- **Appendix**: 5
- **Rectum**: 14
- **Duodenum**: 3
- **Jejunum**: 2
- **Ileum**: 15
- **NOS**: 8
- **Other**: 0.5
Cause of neuroendocrine tumours?

- Exact cause or risk factors are unknown
- Rare genetic conditions
  - MEN1
    - Parathyroid
    - Pituitary
    - Adrenal
Diagnosis
Clinical Symptoms

**Functioning:**
- Tumour produces hormones and/or “proteins/peptides” that cause symptoms

**Non-functioning tumour:**
- Tumours in general do not produce hormones
- Tumour may produce hormones, but patient has no symptoms
Neuroendocrine Tumour Classification: Functioning

- Functioning Neuroendocrine Tumours
  - 40%
- Non-functioning Neuroendocrine Tumours
  - 60%

- Functioning Pancreatic Neuroendocrine Tumours
  - 30%
- Non-functioning Pancreatic Neuroendocrine Tumours
  - 70%
Carcinoid Syndrome: Clinical Presentation

- Telangiectasia (25%)
- Flushing (63–94%)
- Bronchoconstriction (3–19%)
- Cardiac disease (14–41%)
- Abdominal pain (10–55%)
- Cyanosis (18%)
- Diarrhea (68–84%)
- Telangiectasia (25%)
- Arthritis (7%)
- Dermatitis (5%)

Previously used to describe “slow-growing” Neuroendocrine tumour
Does not adequately describe what we know about these tumours today
## Presentations of PNET

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Symptoms</th>
<th>Cell type</th>
<th>% of Mets</th>
<th>location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulinoma</td>
<td>Hypoglycemia</td>
<td>B cell</td>
<td>&lt;15%</td>
<td>pancreas</td>
</tr>
<tr>
<td>Glucagonoma</td>
<td>Rash, (necrotizing migratory erythemia), cachexia</td>
<td>Alpha cell</td>
<td>Majority</td>
<td>pancreas</td>
</tr>
<tr>
<td>VIPoma</td>
<td>Profound secretory diarrhea,</td>
<td>Non-B cell</td>
<td>Majority</td>
<td>Usually pancreas</td>
</tr>
<tr>
<td>Gastinoma</td>
<td>PUD, “ulcers” acid hypersecretion</td>
<td>Non-B cell</td>
<td>&lt;50%</td>
<td>duodenum</td>
</tr>
<tr>
<td>Somatostatinoma</td>
<td>Mass effect</td>
<td>Theta cell</td>
<td>Marjority</td>
<td>pancreas</td>
</tr>
</tbody>
</table>
## Presentation of NET tumors

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>Cough, hemoptysis, Cushing syndrome</td>
</tr>
<tr>
<td>Esophageal/Gastric</td>
<td>Swallowing trouble</td>
</tr>
<tr>
<td></td>
<td>Bleeding, pain</td>
</tr>
<tr>
<td>Bowel</td>
<td>Pain</td>
</tr>
<tr>
<td></td>
<td>Obstruction</td>
</tr>
<tr>
<td>Appendix</td>
<td>Usually incidentally found</td>
</tr>
<tr>
<td>Rectal</td>
<td>Bleeding, constipation</td>
</tr>
</tbody>
</table>
Diagnosis = Pathology

**Biopsy**
- Tumour site
- Neuroendocrine
- Special stains
  - Chromogranin
  - Synaptophysin
- Differentiation
- Grade
  - Ki-67
  - Mitotic rate

**Surgery**
- Lymph nodes
- Margins
- Size
- Lymphovascular invasion
- Perineural invasion
Example

- Post right hemi-colectomy for appendix NET
- PATH
  - 3 cm well differentiated neuroendocrine tumour (T2)
  - Mitosis 1/10 HPF
  - Ki-67<=2%
  - Extension into mesoappendix
  - Negative margins
  - No regional Lymph nodes (0/15)
  - +LVI, Indeterminant Perineural
Identification of Neuroendocrine Cells

- NE cells can be recognized
  - pyramidally shaped
  - Clear cells lying along the basement membrane.

- Special IHC stains:
  synaptophysin, chromogranin, CD56, CD57, CDX2 and SSR2A (somatostatin receptor type 2A)

- IHC for specific hormones:
  insulin, glucagon, somatostatin, gastrin etc
Proliferation activity of NET

1. Ki-67 protein
   - Positive in dividing cells
   - Correlate with faster growing tumour
   - Ex Ki67 2% vs 90%

2. Mitotic rate
   - Count the number of dividing cells
   - Ex. Mitosis = 1/10HPF
Tumor heterogeneity KI67 count 2000 cells in “hot spots”
Pathology report

- **Differentiation**
- **Normal cells**
  - How a less specialized cell becomes more specialized
- **Cancer**
  - How closely the cancer cell looks like the parent cell
  - More poorly differentiated more often cancer will spread and will be faster growing
  - Linked with grade of the cancer
WHO Classification Groups NETs by Diagnostic Factors

<table>
<thead>
<tr>
<th>Differentiation</th>
<th>Well-differentiated neuroendocrine tumor</th>
<th>Well-differentiated neuroendocrine tumor</th>
<th>Poorly differentiated neuroendocrine carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade</td>
<td>G1 Low</td>
<td>G2 Intermediate</td>
<td>G3 High</td>
</tr>
<tr>
<td>Mitotic count</td>
<td>&lt;2 per 10 HPF</td>
<td>2-20 per 10 HPF</td>
<td>&gt;20 per 10 HPF</td>
</tr>
<tr>
<td>Ki-67 index (%)</td>
<td>&lt;3%</td>
<td>3-20%</td>
<td>&gt;20%</td>
</tr>
</tbody>
</table>

Prognosis of Patients With NETs

- Good
- Poor

Counted in 10 high power fields. 10 HPF=2mm², at least 40 fields (400x magnification) in areas of highest density. Ki-67 assessed by MIBI antibody stain; percent positive after count of 2000 cells in area of highest nuclear labelling.

Bosman et al. WHO Classification of Neuroendocrine tumours of the Digestive System, Lyon France IARC Press, 2010, endorsed by ENETS
Other tests

Staging Workup
Biomarker

- **Definition:**
  - Something measurable that indicates a disease state
Caution of Bio-marker tests

- Patient needs to follow test directions
- There are many factors that can cause “false positive” test
  - Diet
  - Medications
  - Other illnesses
- There can be “false negative test”
- Often there is a normal amount in body: Cut-off?
Biomarkers

Look for rises

Correlate
Biomarkers

Blood
• Chromagranin

Urine
• 5HIAA
  • Serotonin
• Metanephrines
  • Pheochromocytoma
• Catecholamines
  • Pheochromocytoma
Staging Tests: Cancer that has travelled

- CT or MRI
  - Looking for a measurable cancer
Nuclear Medicine scan: Functional

Octreotide Scan
- Octreotide, a drug similar to somatostatin, is radiolabelled with indium-111
  - injected into a vein and attaches to tumour cells that have receptors for somatostatin. A radiation-measuring device detects the radioactive octreotide.

MIBG scan
- metaiodobenzylguanidine or mIBG, radiopharmaceutical similar to noradrenaline.
US of Heart

- Carcinoid heart disease
- Pathology:
  - Correlate with Urine 5HIAA
  - Thickening of right heart valves due to formation of fibrotic plaques
  - Affects valve function
**Staging = Pathology + imaging**

<table>
<thead>
<tr>
<th>Primary tumor (T)*</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor 2 cm or less in greatest dimension</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor 1 cm or less in greatest dimension</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor more than 1 cm but not more than 2 cm</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor more than 2 cm but not more than 4 cm or with extension to the cecum</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor more than 4 cm or with extension to the ileum</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor directly invades other adjacent organs or structures, e.g., abdominal wall and skeletal muscle</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regional lymph nodes (N)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph node metastasis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distant metastasis (M)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

**pN0.** Histological examination of a regional lymphadenectomy specimen will ordinarily include 12 or more lymph nodes. If the lymph nodes are negative, but the number of nodes is less than 12, the stage is classified as pN0.

<table>
<thead>
<tr>
<th>Anatomic stage/prognostic groups</th>
<th>T1</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2, T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>
Other classification of NETS: Embryonic Origin

- Foregut
  - Lungs + bronchi
  - Stomach
- Midgut
  - Small intestine
  - Appendix, proximal large bowel
- Hindgut
  - Distal Colon
  - Rectum
  - Genitourinary origin
- Pancreatic
- Other
Conclusions

- NETs are rare, but increasing in number
- Some patients have functional tumours
- Staging based on Pathology (with grading/differentiation) plus imaging
- Biomarkers need to be interpreted in context of other clinical factors
- NETs can be varied and have different clinical behaviour
What Does a Multi-Disciplinary Team Look Like?
Thanks