NETs

CSGNA
25 September 2015, Moncton

The Moncton Hospital

Peter Lightfoot MD FRCPC
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Weir fishing, Grand Manan, N.B –

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Weir fishing, Grand Manan, N.B – like G.I.s, fish also are attracted to any orifice!

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We ❤️ G.I. nurses!

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Notes on Erotica and Tumultuous Sex
NETs

Neuroendocrine Tumors

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Historically:
NETs

Historically:

1897 Kulchitsky – enterochromaffin cell
1907 Oberndorfer – “karznoide” tumor
NETs

Historically:
• Cells with:
  Neural connections
NETs

Historically:

• Cells with:
  
  Neural connections
  
  Production and secretion of chemicals
    
    (“hormones”)

  Amine precursor uptake and decarboxylation (“APUDomas”)
NETs

• Neuroendocrine cells in almost all tissues
NETs

- Neuroendocrine cells in almost all tissues
- Now defined by characteristic microscopy
NETs

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- Now defined by characteristic microscopy
NETs

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• Now defined by characteristic microscopy
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• Now defined by characteristic microscopy

Cytology
NETs

- Neuroendocrine cells in almost all tissues
- Now defined by characteristic microscopy

Chromogranin
NETs

- Neuroendocrine cells in almost all tissues
- Now defined by characteristic microscopy

Synaptophysin
NETs

- Neuroendocrine cells in almost all tissues
- Now defined by characteristic microscopy
- Tumors from everywhere
  - skin (Merkel cell)
  - lung
  - thymus
  - endocrine glands
NETs

- Neuroendocrine cells in almost all tissues
- Now defined by characteristic microscopy
- Tumors from everywhere
  - skin (Merkel cell)
  - lung
  - thymus
  - endocrine glands, such as GI tract:
NETs

- Neuroendocrine cells in almost all tissues
- Now defined by characteristic microscopy
- Tumors from everywhere
  - skin (Merkel cell)
  - lung
  - thymus
  - endocrine glands, such as
    - GI tract: 14 endocrine types
    - 33 amines
NETs

- Neuroendocrine cells in almost all tissues
- Now defined by characteristic microscopy
- Tumors from everywhere
  - skin (Merkel cell)
  - lung
  - thymus
  - endocrine glands, such as gastroenteropancreatic (GEP) NETs
NETs

- Neuroendocrine cells in almost all tissues
- Now defined by characteristic microscopy
- Tumors from everywhere
  - skin
  - lung
  - thymus
  - endocrine glands
  - gastrointestinal (GEP) NETs
NETs

- Gastroenteropancreatic (GEP) NETs
  “Rare”:
NETs

• Gastroenteropancreatic (GEP) NETs
  “Rare”:
  2% of all GI malignancies
NETs

- Gastroenteropancreatic (GEP) NETs
  “Rare”:
  
  2% of all GI malignancies
  75% are carcinoids
NETs

- Gastroenteropancreatic (GEP) NETs

  "Rare":
  
  2% of all GI malignancies
  75% are carcinoids
  non-carcinoid incidence 0.4-1.5/10^5
NETs

• Gastroenteropancreatic (GEP) NETs
  “Rare”:
  2% of all GI malignancies
  75% are carcinoids
  non-carcinoid incidence 0.4-1.5/10^5

Increasing incidence:
NETs

- Gastroenteropancreatic (GEP) NETs
  - “Rare”:
    - 2% of all GI malignancies
    - 75% are carcinoids
    - non-carcinoid incidence 0.4-1.5/10^5
  
  Increasing incidence:
  - 2.1 $\rightarrow$ 9.3/10^5 from 1973 to 2004
NETs

- Gastroenteropancreatic (GEP) NETs
  
  "Rare":

  2% of all GI malignancies
  75% are carcinoids
  non-carcinoid incidence 0.4-1.5/10^5

  Increasing incidence:
  2.1 → 9.3/10^5 from 1973 to 2004
  ? due to improved detection
NETs

- Gastroenteropancreatic (GEP) NETs
  "Rare":
  2% of all GI malignancies
  10-15% are hereditary:
NETs

- Gastroenteropancreatic (GEP) NETs
  - “Rare”:
    - 2% of all GI malignancies
    - 10-15% are hereditary:
      - multiple endocrine neoplasia –
        - MEN1: Werner’s syndrome
          - pituitary
          - parathyroid
          - pancreas
NETs

• Gastroenteropancreatic (GEP) NETs
  “Rare”:
  2% of all GI malignancies
  10-15% are hereditary:
  multiple endocrine neoplasia –
  MEN2: Sipple syndrome
  thyroid
  parathyroid
  adrenal
  pancreas
NETs

- Gastroenteropancreatic (GEP) NETs
  “Rare”:
  - 2% of all GI malignancies
  - 10-15% are hereditary:
    multiple endocrine neoplasia – MEN1, MEN2
    neurofibromatosis type 1
NETs

- Gastroenteropancreatic (GEP) NETs
  
  "Rare":

Quasimodo - ?von Recklinghausen’s disease (NF-1)
NETs

- Gastroenteropancreatic (GEP) NETs
- "Rare":
  - 2% of all GI malignancies
  - 10-15% are hereditary:
    - multiple endocrine neoplasia – MEN1, MEN2
    - neurofibromatosis type 1
    - Von Hippel Lindau
NETs

- Gastroenteropancreatic (GEP) NETs
  “Rare”:
  - 2% of all GI malignancies
  - 10-15% are hereditary:
    - multiple endocrine neoplasia – MEN1, MEN2
    - neurofibromatosis type 1
    - Von Hippel Lindau
      - CNS, hemangioblastomas
      - renal CA, pheo’s, NETs
NETs

• Gastroenteropancreatic (GEP) NETs
  “Rare”:
  
  2% of all GI malignancies
  10-15% are hereditary:
  
  multiple endocrine neoplasia –
  MEN1, MEN2
  
  neurofibromatosis type 1
  Von Hippel Lindau
  Carney complex
NETs

- Gastroenteropancreatic (GEP) NETs
  “Rare”:
  - 2% of all GI malignancies
  - 10-15% are hereditary:
    - multiple endocrine neoplasia – MEN1, MEN2
    - neurofibromatosis type 1
    - Von Hippel Lindau
    - Carney complex
    - heart, lentiginosis, endocr.
NETs

• Gastroenteropancreatic (GEP) NETs “Rare”:
  2% of all GI malignancies
  10-15% are hereditary:
    multiple endocrine neoplasia – 
      MEN1, MEN2
    neurofibromatosis type 1
    Von Hippel Lindau
    Carney complex
    tuberous sclerosis
NETs

• Gastroenteropancreatic (GEP) NETs

  “Rare”:

  2% of all GI malignancies
  10-15% are hereditary:

  multiple endocrine neoplasia –
  MEN1, MEN2
  neurofibromatosis type 1
  Von Hippel Lindau
  Carney complex
  tuberous sclerosis skin, NETs, etc
NETs

- Gastroenteropancreatic NETs
  - Non-functioning
  - Functioning
NETs

- Gastroenteropancreatic NETs
  - Non-functioning >60% (no hormone effect)
  - Functioning
NETs

- Gastroenteropancreatic NETs
  - Non-functioning >60% (no hormone effect)
  - Functioning “oma’s”
NETs

• Gastroenteropancreatic NETs
  Non-functioning >60% (no hormone effect)
  Functioning “oma’s”: serotonin (carcinoids)
NETs

• Gastroenteropancreatic NETs
  Non-functioning  >60% (no hormone effect)
  Functioning “oma’s”: serotonin (carcinoids)
  insulin
NETs

- Gastroenteropancreatic NETs
  - Non-functioning >60% (no hormone effect)
  - Functioning “oma’s”: serotonin (carcinoids)
    - insulin
    - gastrin
NETs

- Gastroenteropancreatic NETs
  - Non-functioning >60% (no hormone effect)
  - Functioning “oma’s”: serotonin (carcinoids)
  - insulin
  - gastrin
  - glucagon
NETs

• Gastroenteropancreatic NETs
  Non-functioning  >60% (no hormone effect)
  Functioning “oma’s”: serotonin (carcinoids)
    insulin
    gastrin
    glucagon
    vasoactive intestinal peptide
NETs

• Gastroenteropancreatic NETs
  Non-functioning >60% (no hormone effect)
  Functioning “oma’s”: serotonin (carcinoids)
    insulin
    gastrin
    glucagon
    vasoactive intestinal peptide
    somatostatin
NETs

• Gastroenteropancreatic NETs
  Non-functioning >60% (no hormone effect)
  Functioning “oma’s”: serotonin (carcinoids)
    insulin
    gastrin
    glucagon
    vasoactive intestinal peptide
    somatostatin
    others (ACTH, PTH, GRF, neurotensin, calcitonin)
NETs

• Presentation:
NETs

• Presentation:
  obstruction, bleeding, mass
NETs

• Presentation:
  obstruction, bleeding, mass metastases
NETs

- Presentation:
  - obstruction, bleeding, mass
  - metastases
  - syndromic (from hormones)
NETs

- Presentation:
  obstruction, bleeding, mass metastases
  syndromic (from hormones)
  incidental finding
NETs

• Diagnosis
NETs

- Diagnosis: scopes
NETs

- Diagnosis: scopes
capsule endoscopy
NETs

- Diagnosis: scopes
  capsule endoscopy
  CT
NETs

- Diagnosis: scopes
  capsule endoscopy
  CT
  ultrasound
NETs

- Diagnosis: scopes
capsule endoscopy
CT
ultrasound
MRI
NETs

- Diagnosis: scopes
capsule endoscopy
CT
ultrasound
MRI
PET scan
NETs

- Diagnosis:
  - scopes
  - capsule endoscopy
  - CT
  - ultrasound
  - MRI
  - PET scan
  - octreotide scan
NETs

- Diagnosis:
  - Scopes
  - Capsule endoscopy
  - CT
  - Ultrasound
  - MRI
  - PET scan
  - Octreotide scan
  - EUS
NETs

- Diagnosis:
  - scopes
  - capsule endoscopy
  - CT
  - ultrasound
  - MRI
  - PET scan
  - octreotide scan
  - EUS
  - biopsy
NETs

- Diagnosis:
  - Capsule endoscopy
  - CT
  - Ultrasound
  - MRI
  - PET scan
  - Octreotide scan
  - EUS biopsy

Micrograph of a neuroendocrine tumor. H&E stain.
NETs

- Management
NETs

- Management
- Early detection
NETs

• Management
  Early detection (average delay 4-6 yr)
NETs

- Management
  - Early detection (average delay 4-6 yr)
  - Accurate classification
NETs

• Management
  Early detection (average delay 4-6 yr)
  Accurate classification
  Multidisciplinary approach
NETs

• Management
  Early detection (average delay 4-6 yr)
  Accurate classification
  Multidisciplinary approach
  Aggressive treatment where appropriate
NETs

- Treatment
NETs

- Treatment
  Observation only
NETs

- Treatment
  - Observation only
  - Surgery for cure
NETs

• Treatment
  Observation only
  Surgery for cure
  Surgery for symptom relief (incl. debulking)
NETs

• Treatment
  Observation only
  Surgery for cure
  Surgery for symptom relief (incl. debulking)
  Endovascular surgery, RFA, EtOH injection
NETs

• Treatment
  Observation only
  Surgery for cure
  Surgery for symptom relief (incl. debulking)
  Endovascular surgery, RFA, EtOH injection
  Block hormone - octreotide (may debulk)
NETs

- Treatment
  - Observation only
  - Surgery for cure
  - Surgery for symptom relief (incl. debulking)
  - Endovascular surgery, RFA, EtOH injection
  - Block hormone - octreotide (may debulk)
  - Block effect - diazoxide (insulin)
  - Proton pump inhibitor
NETs

- **Treatment**
  - Observation only
  - Surgery for cure
  - Surgery for symptom relief (incl. debulking)
  - Endovascular surgery, RFA, EtOH injection
  - Block hormone - octreotide (may debulk)
  - Block effect - diazoxide (insulin)
  - proton pump inhibitor
- Chemotherapy
NETs

- **Treatment**
  - Observation only
  - Surgery for cure
  - Surgery for symptom relief (incl. debulking)
  - Endovascular surgery, RFA, EtOH injection
  - Block hormone - octreotide (may debulk)
  - Block effect - diazoxide (insulin)
  - Proton pump inhibitor
  - Chemotherapy
  - Biological targeting
NETs

• Prognosis
NETs

- Prognosis
  Tend to be slow growing
NETs

• Prognosis
  Tend to be slow growing
  JF

1975
NETs

• Prognosis
  Tend to be slow growing
  JF

? 1975
NETs

• Prognosis
  Tend to be slow growing
  JF

2005
NETs

- Prognosis
  Tend to be slow growing
NETs

- Prognosis
  Tend to be slow growing

JF 2005
NETs

- Prognosis
  Tend to be slow growing
NETs

• Prognosis

Tend (....) to be slow growing, but -
NETs

- Prognosis

Tend (…. ) to be slow growing, but - EF

Oct 2013
NETs

- Prognosis

Tend (....) to be slow growing, but -

EF

Oct 2013
NETs

- Prognosis
  
  Tend (....) to be slow growing, but -
  
  EF

Mar 2014
• **Prognosis**

  *Tend (…) to be slow growing, but - EF*

  Mar 2014
NETs

• Prognosis

Tend (....) to be slow growing, but -

EF

Aggressive

Mar 2014
NETs

• Prognosis

Tend (.....) to be slow growing but not all, therefore need - Grading System

<table>
<thead>
<tr>
<th>Grade</th>
<th>Lung and Thymus (WHO)\textsuperscript{14}</th>
<th>GEP-NETs (ENETS, WHO)\textsuperscript{28,29}</th>
<th>Lung and Thymus (Moran et al)\textsuperscript{33}</th>
<th>Pancreas (Hochwald et al)\textsuperscript{14}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low grade</td>
<td>&lt;2 mitoses / 10 hpf AND no necrosis</td>
<td>&lt;2 mitoses / 10 hpf AND &lt;3% Ki67 index</td>
<td>≤3 mitoses / 10 hpf AND no necrosis</td>
<td>&lt;2 mitoses / 50 hpf AND no necrosis</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2–10 mitoses / 10 hpf OR foci of necrosis</td>
<td>2–20 mitoses / 10 hpf OR 3%–20% Ki67 index</td>
<td>4–10 mitoses / 10 hpf OR foci of necrosis</td>
<td>2–50 mitoses / 50 hpf OR foci of necrosis</td>
</tr>
<tr>
<td>High grade</td>
<td>&gt;10 mitoses / 10 hpf</td>
<td>&gt;20 mitoses / 10 hpf OR &gt;20% Ki67 index</td>
<td>&gt;10 mitoses / 10 hpf, Necrosis present</td>
<td>&gt;50 mitoses / 50 hpf</td>
</tr>
</tbody>
</table>
NETs

• Prognosis
  5 yr survival 1988 for pNET with mets 40%
NETs

• Prognosis

  5 yr survival 1988 for pNET with mets 40%
  " " 2002 " " " " 82%
NETs - summary
NETs - summary

• Characteristic cell types – need biopsy
NETs - summary

- Characteristic cell types – need biopsy
  - but may suspect a NET by:
    - clinical presentation
    - imaging features (round, localized, vascular)
    - serum markers (chromogranin A, hormones)
NETs - summary

- Characteristic cell types – need biopsy
- Uncommon but increasing occurrence
- Unusual “hormone” syndromes
- Most slow-growing
- Found incidentally
- Only cure is surgery, but “may outlive tumor”
- Exciting new advances
NETs - summary

Thank you
NETs - summary

Thank you
NETs - summary

Thank you

When you are in class and you find how fascinating

The window is
NETs - summary
Thank you for staying awake
NETs - summary

Thank you for staying awake

....... the quiz starts now