GI and Pancreatic NETs

Disclosures
- Ipsen NET Advisory Board

Histologic classification

<table>
<thead>
<tr>
<th>Differentiation</th>
<th>Grade</th>
<th>Mitotic Count</th>
<th>Ki-67 Index (%)</th>
<th>Traditional Classification</th>
<th>ENETS, WHO Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well-differentiated</td>
<td>Low (G1)</td>
<td>≤ 2 per 10 HPF</td>
<td>≤ 2</td>
<td>Carcinoid, islet cell, pancreatic neuroendocrine tumor</td>
<td>Neuroendocrine tumor, grade 1</td>
</tr>
<tr>
<td></td>
<td>Intermed. (G2)</td>
<td>2-20 per 10 HPF</td>
<td>3-20</td>
<td>Carcinoid, atypical carcinoid, islet cell, pancreatic neuroendocrine tumor</td>
<td>Neuroendocrine tumor, grade 2</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>High (G3)</td>
<td>&gt; 20 per 10 HPF</td>
<td>&gt; 20</td>
<td>Small cell carcinoma</td>
<td>Neuroendocrine carcinoma, grade 3, small cell</td>
</tr>
</tbody>
</table>

ENETS, European Neuroendocrine Tumor Society; WHO, World Health Organization; HPF, high-power fields.
GI and Pancreatic Neuroendocrine tumors (NETs)

Diverse diseases
- Insulinoma
- Gastrinoma
- Small intestine NET (carcinoid)
- Nonfunctioning pancreatic NET (NF-PNET)
- Others...

CASE 1
Laparoscopic enucleation of insulinoma

CASE 2
Multifocal NETs (N = 18) in ileum (carcinoid)

CASE 3
Duodenal gastrinoma
CASE 4

Whipple procedure for NF-PNET

CASE 5

Total pancreatectomy for NF-PNET (12 cm)

GI and Pancreatic Neuroendocrine tumors (NETs)

Overview

- Focus on a very confusing issue in NETs
  - NETs of Unknown Primary
- It’s not so confusing after all
- History and experience have shone us the light
- Seeing is believing
If you remember only two things
• NETs of unrecognized primary site are typically *hiding* in the ileum
• NETs of the ileum are often multifocal → must *palpate*

What does “unknown primary” mean?
• The location where the NET originated is not known.
NETs of Unknown Primary

What does “unknown primary” mean?

• The location where the NET originated is not known

• Possible primary sites:
  • Small intestine (ileum, jejunum, duodenum)
  • Pancreas
  • Colon/rectum
  • Bronchopulmonary
  • Stomach...

NETs of Unknown Primary

Does finding the primary tumor matter?

Reasons for finding the primary tumor

• Symptoms
  • Abdominal pain, weight loss

• Asymptomatic
  • Resect the primary as part of surgery to remove all gross disease
  • Prevent bowel obstruction
  • Prevent ischemia
  • Improve outcome?

Hellman et al. World J Surg 2002
Givi et al. Surgery 2006

Small intestine (ileum) NET

Intestinal ischemia
Small intestine (ileum) NET

**Intestinal ischemia**

Small intestine (ileum) NET

**Intestinal obstruction**

NETs of Unknown Primary

**Reasons for finding the primary tumor**

- Treatment increasingly depends on site
- Everolimus, sunitinib for pancreatic NETs
- Octreotide for well differentiated midgut NETs
- Lanreotide for well-differentiated NF GI and pancreatic NETs
- Systemic chemotherapy for pancreatic NETs
- Participation in clinical trials

Bergsland and Nakakura. JAMA Surg 2014
What tests should be done to find it?

- CT?
- MRI?
- OctreoScan?
- $^{68}\text{Ga-DOTA-TATE}$ or $^{68}\text{Ga-DOTA-NOC}$ PET-CT
- Upper/lower endoscopy?
- Endoscopic ultrasound?
- Enteroclysis?
- Capsule endoscopy?
- Double-balloon enteroscopy?
- Gene expression profiling?

**UCSF study**

- **Study design**: Pathology database (1993-2008)
- **Setting**: UCSF
- **Patients**: 123 patients with NET liver metastases
- **Outcomes**: 1) Detection of primary tumor preop 2) Laparoscopic or open surgery to find and remove an unknown primary tumor

Wang et al. Arch Surg 2010
NETs of Unknown Primary

**UCSF study**

<table>
<thead>
<tr>
<th>Diagnostic Method</th>
<th>No of Studies</th>
<th>Primary identified (sensitivity, No. %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Computed tomography</td>
<td>76</td>
<td>27 (34.6)</td>
</tr>
<tr>
<td>Magnetic resonance imaging</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Somatostatin receptor tomography</td>
<td>42</td>
<td>11 (26.2)</td>
</tr>
<tr>
<td>PET scan</td>
<td>6</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Endoscopy</td>
<td>21</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>Stomach NET</td>
<td>1</td>
<td>1 (100%)</td>
</tr>
<tr>
<td>Lower endoscopy</td>
<td>42</td>
<td>20 (47.6)</td>
</tr>
<tr>
<td>All colon/ileum NET</td>
<td>33</td>
<td>20 (60.6)</td>
</tr>
<tr>
<td>Colonic NET</td>
<td>15</td>
<td>13 (86.7)</td>
</tr>
<tr>
<td>Rectal NET</td>
<td>18</td>
<td>7 (38.9)</td>
</tr>
<tr>
<td>Capsule endoscopy</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Small bowel series</td>
<td>1</td>
<td>1 (100%)</td>
</tr>
<tr>
<td>Ultrasonography</td>
<td>3</td>
<td>0</td>
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- Despite extensive evaluation, 13.8% had occult primary tumors.

**Siegfried Oberndorfer**

(1876-1944)

- 1907: Pathological Institute of Geneva
  - 1) multiple tumors in submucosa of ileum
  - 2) slow growth
  - 3) borders sharply circumscribed
  - 4) (do not metastasize)

- Karzinoide: “carcinoma-like”

- 1929: He recognized potential to metastasize

**Gastrointestinal NETs Epidemiology**

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<td>Stomach</td>
<td>2.5</td>
<td>7</td>
</tr>
<tr>
<td>Small intestine</td>
<td>25</td>
<td>44</td>
</tr>
<tr>
<td>Appendix</td>
<td>48</td>
<td>7</td>
</tr>
<tr>
<td>Colon</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>Rectum</td>
<td>17</td>
<td>24</td>
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Wang et al. Arch Surg 2010

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Modlin et al. Arch Surg 2010
NETs of Unknown Primary

UCSF study results

• Primary site found in 13/15 patients (87%) by surgery
• All primary tumors in small intestine (12 ileum, 1 jejunum)
• Primary tumors small (1.4 cm) and often multifocal (54%)
• Careful palpation of small intestine is essential

Wang et al. Arch Surg 2010

Multicenter results

<table>
<thead>
<tr>
<th>Institution</th>
<th>Year</th>
<th>No. of Unknown Primary</th>
<th>Primary Identified</th>
<th>Location of Primary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Louisiana State University</td>
<td>2005</td>
<td>22</td>
<td>17 (77.3)</td>
<td>Not specified</td>
</tr>
<tr>
<td>Health Sciences Center</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>University of California</td>
<td>2010</td>
<td>15</td>
<td>13 (86.7)</td>
<td>12 ileum, 1 jejunum</td>
</tr>
<tr>
<td>San Francisco</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oregon Health and</td>
<td>2012</td>
<td>52</td>
<td>39 (75.0)</td>
<td>Most in small intestine</td>
</tr>
<tr>
<td>Science University</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>University of Pennsylvania</td>
<td>2013</td>
<td>26</td>
<td>25 (96.3)</td>
<td>Terminal ileum, 12 other small intestine</td>
</tr>
<tr>
<td>University of Pennsylvania</td>
<td>2013</td>
<td>17</td>
<td>17 (100.0)</td>
<td>23 ileum, 3 pancreas</td>
</tr>
<tr>
<td>Health Sciences Center</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>143</td>
<td>128 (89.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

~ 84% success in finding primary
Bergsland and Nakakura. JAMA Surg 2014

NETs of Unknown Primary

Laparoscopic identification of tumor in ileum

Wang et al. Arch Surg 2010

Karnovsky Memorial Lecture

An Odyssey in the Land of Small Tumors

• Small intestine NETs
  – Most (193/209; 92%) arise from ileum
  – Multifocal (46/183; 25%)
• Primary tumors small, deep mucosal site of origin
• Nature of spread
  – First invades muscle layer → serosa → mesentery (outward spread)
• Nature of obstruction
  – Fibroblastic reaction in mesentery → buckling of bowel wall → kinking of bowel wall (like an accordion)

Moertel CG. J Clin Oncol 1987
NETs of Unknown Primary

Laparoscopic identification of tumor in ileum

NETs of Unknown Primary

Laparoscopic identification of tumor in ileum with Meckel's diverticulum

NETs of Unknown Primary

Laparoscopic identification of tumor in ileum with regional adenopathy

NETs of Unknown Primary

Multifocal primary tumors (N = 11) in ileum
NETs of Unknown Primary

Multifocal primary tumors (N = 11) in ileum

Multifocal primary tumors (N = 11) in ileum (#2)
NETs of Unknown Primary

What tests should be done to find it?
- CT scan: chest, abdomen/pelvis (multiphase, thin slice)
- Somatostatin receptor scintigraphy (OctreoScan)
- Urine 24-h 5-HIAA
- Upper and lower endoscopy
- Immunohistochemical markers (TTF-1, CDX2, PAX8, Islet 1)
- Careful review by multidisciplinary team

Finding the Primary Tumor

Potentially seen on colonoscopy
- terminal ileum NET

Finding the Primary Tumor

Potentially seen on colonoscopy
- terminal ileum NET

NETs of Unknown Primary

Take home points
- For most patients with WD-NETs and unknown primary the primary site is most likely in the ileum
- If surgery planned, appropriate preoperative tests should be done
- Many other tests (enteroclysis, capsule endoscopy, double-balloon enteroscopy, and endoscopic ultrasound) unnecessary since will not affect patient care and only delay treatment
- Must carefully palpate small intestine because ileum NETs are frequently multifocal
NETs of Unknown Primary

*Patient example*
- A 60-year-old man
- Fall 2008: abdominal pain
- Evaluated at a local hospital

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NETs of Unknown Primary

*Patient example*
- Bilobar liver masses
- Core needle biopsy: CgA +, Syn +
- Well-differentiated NET
- Unknown primary site

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NETs of Unknown Primary

*Patient example*
- A 60-year-old man with NET liver metastases and unknown primary
- Fall 2008: Started Sandostatin
- Patient informed his disease was inoperable
- UCSF for second opinion by multidisciplinary GI oncology group

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NETs of Unknown Primary

*Patient example*
- Winter 2008:
- Laparoscopic identification and resection of ileum primary tumor

Wang et al. Arch Surg 2010
**NETs of Unknown Primary**

*Patient example*

- A 60-year-old man with NET liver metastases and unknown primary
- **Fall 2008:** Started Sandostatin
- **Winter 2008:** Primary found and removed
- **Fall 2009:** Carcinoid syndrome
  
  Liver metastases stable

---

**NETs of Unknown Primary**

*Patient example*

- **Winter 2009:**
  - Right hepatectomy and microwave ablation of two left lobe tumors
  - Carcinoid syndrome resolved

---

**NETs of Unknown Primary**

*Patient example*

- A 60-year-old man with NET liver metastases and unknown primary
- **Fall 2008:** Started Sandostatin
- **Winter 2008:** Primary found and removed
- **Winter 2009:** Resection/ablation of liver mets
- **Dec. 2014:** No evidence of disease

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**NETs of Unrecognized Primary**

NETs arising from the ileum