Incidental Appendiceal Tumors

Roseanna Lee
SUNY - Downstate
December 22, 2011
32 year old female presents to the ED in August 2011 with one week history of right lower quadrant pain. She describes the pain as intermittent, sharp, radiating to suprapubic region, associated with nausea and diarrhea. She has history of intermittent RLQ pain since May 2011, which she was evaluated for in the ED and dx with PID. She was worked up as outpatient for GYN pathology, workup was negative.

- PMH: asthma
- PSH: none
- Meds: Albuterol PRN
- NKDA
- Social: ex-smoker, 5pk yr history
Vitals:
- T 98.6 BP 100/68 HR 95 R 18 100%
- 5’3, 184lbs
- Abdomen soft, nondistended, +RLQ tenderness, no mass palpable

Labs
- Cbc 10/11/34/500
CT scan
CT scan: Nonfilling, dilated appendix containing multiple appendicololiths with surrounding inflammatory changes
• OR for laparoscopic appendectomy

• Hospital course
  • POD#1 – clears diet
  • POD#2 – diet advanced, discharged home
Pathology

- 2.8cm well differentiated neuroendocrine carcinoma, grade 1
- No lymphovascular or perineural invasion
- Chronic periappendicitis
- Immunohistochemistry stain
  - Positive for synaptophysin and chromogranin
- pT2 pNx PMx
Outpatient workup

- Upper Endoscopy
- Colonoscopy
- Octreotide scan
- Chromogranin A level – 5 nmol/L
- Scheduled for Right hemicolecction in October 2011
Pathology

- Right ileocolectomy
  - Negative for tumor
  - 0/20 Lymph nodes
Questions?
Appendiceal Tumors
Appendiceal Carcinoma

Epidemiology

- Incidence:
  - 0.12 per million
  - 1% of appendectomies
  - 1 in 300 appendectomies

- Most commonly present as acute appendicitis, followed by chronic abdominal pain and RLQ mass

- Preop diagnosis is usually associated with advanced disease

The Appendix

- Derived from midgut
- Appears at 8th week gestation as outpouching of cecum
- Base located at convergence of taeniae
- Length varies 2-20cm, average 9cm
- Blood supply: appendiceal artery, branch of ileocolic artery
- Lymphatic drainage – anterior ileocolic lymph nodes
Primary Appendiceal Carcinoma

- Neuroendocrine tumors (carcinoid)
- Goblet cell carcinoid
- Adenocarcinomas
  - Mucinous – cystadenocarcinomas (Pseudomyxoma peritonei)
  - Colonic
  - Signet-ring
Appendiceal Carcinoid Tumors

- Mean Age and Gender: 38yo, 2.6:1 Female: Male
- Neuroendocrine tumor (Enterochromaffin cell)
- 24% carcinoids in appendix
  - 3rd most common location for carcinoid tumors following small bowel and rectum
- 2nd primary tumor – 18.2%
- Location
  - 60-75% tip of appendix
  - 5-21% mid appendix
  - 7-10% base of appendix
- Size
  - 60-76% <1cm
  - 4-27% 1-2cm
  - 2-17% >2cm

Histology

- Originate from subepithelial neuroendocrine cells
- Immunohistochemistry:
  - Chromogranin A
  - Synaptophysin antibodies
- Proliferation rate
  - Ki-67 marker
Well-differentiated endocrine tumor

- **Benign behavior**
  - Nonfunctioning
  - Confined to appendiceal wall
  - <2cm
  - Nonangioinvasive
  - Ki-67 index <2%
  - Mitoses of <2 cells/high powerfields x40

- **Uncertain behavior**
  - Nonfunctioning
  - Confined to subserosa
  - >2cm
  - Angioinvasive

Malignant well-differentiated endocrine carcinoma – low grade

- Invading mesoappendix or beyond
- Or metastases
- +/- carcinoid syndrome

Mixed exocrine-endocrine carcinoma

- Goblet cell carcinoids
TNM Classification

- European Neuroendocrine Tumor Society (2007)
  - T1 - <1cm, submucosa or muscularis propria
  - T2 - <2cm, <3mm invasion of mesoappendix
  - T3 - >2cm, >3mm invasion of mesoappendix
  - T4 - peritoneum or other organs
  - G1 – Mitotic count <2, Ki-67 index <2%
  - G2 – Mitotic count 2-20, Ki-67 index 3-20%
  - G3 – Mitotic count >20, Ki-67 index >20%

- American Joint Committee on Cancer (2009)
  - T1a - <1cm
  - T1b - 1-2cm
  - T2 - 2-4cm or extension to cecum
  - T3 - >4cm or extension to ileum
  - N0 – no regional lymph node metastasis
  - N1 – regional lymph nodes metastasis
  - M0 – no distant metastasis
  - M1 – distant metastasis
Staging (AJCC)

- **Stage I**
  - T1 N0 M0

- **Stage II**
  - T1 N1 M0
  - T2 N0 M0
  - T3 N0 M0

- **Stage III**
  - T4 N0 M0
  - Any T N1 M0

- **Stage IV**
  - Any I Any N M1
Workup

- Chromogranin A – blood marker found elevated in 80-100% of patients with neuroendocrine tumors
  - Corresponds to tumor load
  - >5000 ug/L predict poor outcome
- Octreotide scan – most sensitive in diagnosis and staging of metastatic disease
- CT Scan
- Endoscopy – high incidence of metachronous and synchronous GI neoplasms (18-33%)
Prognosis

- Prognosis is directly related to size of tumor
- High incidence of lymph node metastasis in tumors >2cm

Table 1. Prognosis of appendiceal endocrine tumours according to size

<table>
<thead>
<tr>
<th>Author</th>
<th>Median follow-up</th>
<th>All patients</th>
<th>Metastases</th>
<th>Patients</th>
<th>&lt;2 cm</th>
<th>&lt;2 cm + mesoappendiceal invasion</th>
<th>&gt;2 cm + mesoappendiceal invasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stinner and Rothmund</td>
<td>n.i.</td>
<td>493</td>
<td>neg</td>
<td>476</td>
<td>361</td>
<td>75</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>pos</td>
<td>17</td>
<td>0 (0%)</td>
<td>5 (6.7%)</td>
<td>12 (30%)</td>
</tr>
<tr>
<td>Moertel et al. [15]</td>
<td>26 years</td>
<td>150</td>
<td>neg</td>
<td>143</td>
<td>104</td>
<td>23</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>pos</td>
<td>7</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>3 (21%)</td>
</tr>
</tbody>
</table>

Prognosis

- Impact of survival with mesoappendix infiltration is controversial
  - Found in 33-57% of cases
  - Studies from Rossi et al and Moertel et al found no recurrent or metastatic disease in pt with mesoappendiceal invasion
  - MacGillivray et al found tumors >2cm and mesoappendiceal invasion related to metastatic disease
**Survival based on Staging**

**Table 4. 5-Year Survival Rates by Carcinoid Location (1973–1997)**

<table>
<thead>
<tr>
<th>Site</th>
<th>All Stages</th>
<th>Local Stage</th>
<th>Regional Stage</th>
<th>Distant Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>75.1%/55.3%</td>
<td>90.2%/69.6%</td>
<td>40.4%/27.2%</td>
<td>18.0%/9.0%</td>
</tr>
<tr>
<td>Small bowel</td>
<td>76.1%/54.6%</td>
<td>94.5%/70.4%</td>
<td>84.4%/64.1%</td>
<td>51.2%/32.4%</td>
</tr>
<tr>
<td><strong>Appendix</strong></td>
<td>76.3%/65.0%</td>
<td>95.6%/87.8%</td>
<td>80.0%/67.6%</td>
<td>37.5%/26.8%</td>
</tr>
<tr>
<td>Colon</td>
<td>69.5%/41.8%</td>
<td>94.1%/77.1%</td>
<td>72.5%/35.3%</td>
<td>27.8%/4.1%</td>
</tr>
<tr>
<td>Rectum</td>
<td>87.5%/77.8%</td>
<td>94.9%/86.2%</td>
<td>53.7%/42.1%</td>
<td>14.6%/13.1%</td>
</tr>
</tbody>
</table>

*Note:* Cancer-specific survival/relative overall survival. Survival rates are all age-adjusted to standard 2000 population.

Management

- < 1cm – appendectomy
- > 2cm – right hemicolectomy
- 1 – 2 cm - ???
  - Mesoappendiceal infiltration
  - Positive or unclear margins
  - Vascular invasion
  - Tumor involving base of appendix

- Two-step approach
  - Timing of hemicolectomy should be performed within 3 months after appendectomy
  - Can be performed by laparoscopic or open approach
  - No data to support two-step approach to have negative impact on prognosis
Follow-up
ENETS Guidelines

- For well-differentiated tumors <1cm and R0 resection, no follow-up is required after surgery.
- For tumors 1-2cm and R0 resection, insufficient data regarding follow-up. Recommend follow-up investigations for high proliferation marker, vascular invasion, deep mesoappendiceal invasion, involvement of base of appendix.
- For well-differentiated tumors >2cm, at all locations of the appendix, imaging follow-up is recommended:
  - CT scan
  - Octreotide scintigraphy
  - Colonoscopy
  - Tumor markers – chromogranin A level, 5-HIAA (carcinoid syndrome)
<table>
<thead>
<tr>
<th>Follow-up</th>
<th>endoscopy</th>
<th>US/CT/MRI</th>
<th>Octreoscan</th>
<th>CgA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign insulinoma</td>
<td>no</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type I gastric carcinoid</td>
<td>yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectal carcinoid</td>
<td>no (if completely resected)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appendiceal carcinoid T1</td>
<td>no</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appendiceal carcinoid T2</td>
<td>? (see text)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resectable tumor (uncertain behavior) G1</td>
<td>every 6–12 months</td>
<td>yes</td>
<td></td>
<td>yes^1</td>
</tr>
<tr>
<td>G1</td>
<td>every 6–12 months</td>
<td>yes</td>
<td></td>
<td>yes^1</td>
</tr>
<tr>
<td>G2</td>
<td>every 6 months</td>
<td>yes</td>
<td>yearly^2</td>
<td>yes</td>
</tr>
<tr>
<td>G3</td>
<td>every 3 months</td>
<td>yes</td>
<td>yearly^2</td>
<td>yes</td>
</tr>
<tr>
<td>Non-resectable malignant tumor with/without nodal involvement and/or liver and other metastases G1</td>
<td>every 6–12 months</td>
<td>yes</td>
<td>every 2 years^2</td>
<td>yes</td>
</tr>
<tr>
<td>G2</td>
<td>every 6 months</td>
<td>yes</td>
<td>yearly^2</td>
<td>yes</td>
</tr>
<tr>
<td>G3</td>
<td>every 3 months</td>
<td>yes</td>
<td>yearly^2</td>
<td>yes^3</td>
</tr>
</tbody>
</table>

^1 Only in the presence of a visible tumor.
^2 Recommendations regarding the time frames of Octreoscan should be adjusted to the individual situation.
^3 In poorly differentiated tumors and negative CgA NSE may act as a suitable marker.

Arnold et al. ENETS Consensus Guidelines for the Standard of Care in Neuroendocrine Tumors: Follow-Up and Documentation.
Goblet Cell Carcinoids

- Adenocarcinoid, mucinous carcinoid, goblet cell tumors
- Introduced in 1970s as a separate entity with mixed histological features that differed from carcinoid and adenocarcinoma
- Distinct prognostic group intermediate between carcinoid tumor and adenocarcinoma
- 5% of all primary appendiceal malignancies
- 1:1 Male:Female ratio
- Median age 58, second peak at 70
- 63% metastases (ovaries, right colon, peritoneum) present at diagnosis
- Commonly presents as acute appendicitis, followed by abdominal pain/mass, bowel obstruction, intussusception, bleeding
Histology

- Mixed phenotype – partial neuroendocrine cell and intestinal type goblet cell
- Mucin-containing, goblet-shaped epithelial cells
- Submucosal growth pattern with sparing of mucosa
- Focal positive immunoreactivity for neuroendocrine markers (chromogranin or synaptophysin)
Workup

- Chest CT
- Abd/pelvis CT
- Octreotide scan
- Endoscopy
- Tumor markers: CEA, CA19-9, CA-125
Prognosis

- Prognosis is dependent on:
  - Size
  - Serosal involvement
  - Mesoappendiceal invasion
  - Histology
  - Stage
Prognosis

- Survival is dependent on histological subtype
  - Typical GCC
  - Adenocarcinoma ex GCC, signet ring cell type
  - Adenocarcinoma ex GCC, poorly differentiated adenocarcinoma cell type

Survival

- SEER data (1973-2001)
- 5 year overall survival 76%
  - Localized 86%
  - Regional 74%
  - Distant 18%
Management

<table>
<thead>
<tr>
<th>Tumor Presentation</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor localized and confined to appendix (pT1 or pT2) and</td>
<td>Insufficient data to recommend</td>
</tr>
<tr>
<td>Typical GCC histology (group A) and</td>
<td></td>
</tr>
<tr>
<td>Negative appendectomy resection margin</td>
<td></td>
</tr>
<tr>
<td>Tumor spread beyond appendiceal wall (pT3 or pT4) or</td>
<td>Right hemicolecotomy</td>
</tr>
<tr>
<td>Histology of an adenocarcinoma (group B or C) or</td>
<td>Consider oophorectomy</td>
</tr>
<tr>
<td>Localized perforation (secondary to inflation) or</td>
<td>Chemotherapy in stage III and IV</td>
</tr>
<tr>
<td>Positive appendectomy resection margin</td>
<td></td>
</tr>
<tr>
<td>Intraperitoneal spread (stage IV) or</td>
<td>Debulking surgery</td>
</tr>
<tr>
<td>Presence of poorly differentiated adenocarcinoma component</td>
<td>Consider oophorectomy</td>
</tr>
<tr>
<td></td>
<td>Systemic and intraperitoneal chemotherapy</td>
</tr>
</tbody>
</table>

Appendiceal Adenocarcinoma

- Mucinous adenocarcinoma
- Colonic type adenocarcinoma
- Signet ring cell adenocarcinoma
Appendiceal Adenocarcinoma

<table>
<thead>
<tr>
<th></th>
<th>Mucinous</th>
<th>Adeno</th>
<th>Carcinoid</th>
<th>Goblet</th>
<th>Signet</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>951 (38)</td>
<td>646 (26)</td>
<td>435 (17)</td>
<td>369 (15)</td>
<td>113 (4)</td>
</tr>
<tr>
<td>Incidence rate(^{a,b})</td>
<td>1.3</td>
<td>0.95</td>
<td>0.63</td>
<td>0.5</td>
<td>0.15</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>60 ± 15</td>
<td>63 ± 16</td>
<td>41 ± 19</td>
<td>52 ± 16</td>
<td>59 ± 14</td>
</tr>
<tr>
<td>Male</td>
<td>47</td>
<td>58</td>
<td>29</td>
<td>51</td>
<td>49</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>78</td>
<td>75</td>
<td>86</td>
<td>82</td>
<td>83</td>
</tr>
<tr>
<td>Black</td>
<td>7</td>
<td>13</td>
<td>8</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Hispanic</td>
<td>8</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Asian</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Tumor size (cm)(^c)</td>
<td>5.2 ± 3.8</td>
<td>3.9 ± 2.5</td>
<td>2.5 ± 2.1</td>
<td>2.4 ± 2.2</td>
<td>4.2 ± 2.5</td>
</tr>
<tr>
<td>Size (cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1</td>
<td>6</td>
<td>8</td>
<td>13</td>
<td>19</td>
<td>6</td>
</tr>
<tr>
<td>&gt;1 to ≤2</td>
<td>17</td>
<td>20</td>
<td>32</td>
<td>32</td>
<td>20</td>
</tr>
<tr>
<td>&gt;2</td>
<td>77</td>
<td>72</td>
<td>55</td>
<td>49</td>
<td>74</td>
</tr>
<tr>
<td>Overall stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localized</td>
<td>28</td>
<td>45</td>
<td>60</td>
<td>64</td>
<td>14</td>
</tr>
<tr>
<td>Regional</td>
<td>21</td>
<td>28</td>
<td>28</td>
<td>24</td>
<td>26</td>
</tr>
<tr>
<td>Distant</td>
<td>51</td>
<td>27</td>
<td>12</td>
<td>12</td>
<td>60</td>
</tr>
</tbody>
</table>

Data are percentages of means ± standard deviations unless otherwise indicated.

\(^a\)Incidence rate per 1,000,000 population from 1973 to 2001.

\(^b\)Age-adjusted.

\(^c\)Data available only for patients from 1988 to 2001.
Mucinous adenocarcinoma

- Malignant mucocele, cystadenocarcinoma
- Rarely spread via lymphatics or hematologically
- Noninvasive characteristic – spreads along serosal surfaces of the viscera
- Half present with disseminated disease - Pseudomyxoma peritonei
- Stephenson et al. (1985) 10 yr survival
  - 37% appendectomy
  - 65% right hemicolecetomy
- Surgical debulking, omentectomy for metastatic disease
  - Chemotherapy and radiotherapy have not been found to be effective
Appendiceal adenocarcinoma

- Colonic type adenocarcinoma
  - Presents in older patients
  - Localized to base of appendix
  - Lymphatic and hematogenous spread
  - Anderson et al. 5 yr survival
    - 46% appendectomy alone
    - 60% right hemicolecotomy

- Signet ring cell type adenocarcinoma
  - Worst prognosis

- Management: Right hemicolecotomy +/- chemotherapy

AJCC TNM Staging

- **Tis** – carcinoma in situ
- **T1** – invades submucosa
- **T2** – invades muscularis propria
- **T3** – invades subserosa or mesoappendix
- **T4a** – invades beyond visceral peritoneum
- **T4b** – invade adjacent organs

- **N0** – no lymph nodes
- **N1** – 1-3 lymph nodes
- **N2** – 4+ lymph nodes

- **M1a** – intraperitoneal mets
- **M1b** – nonperitoneal distant metastasis

- **Stage 0** – carcinoma insitu
- **Stage I**
  - T1 N0 M0
  - T2 N0 M0
- **Stage IIa** T3 N0 M0
- **Stage IIb** T4a N0 M0
- **Stage IIc** T4b N0 M0
- **Stage IIIa** T1/T2 N1 M0
- **Stage IIIb** T3/T4 N1 M0
- **Stage IIIc** any T N2 M0
- **Stage IVa** any T N0 M1a
- **Stage IVb**
  - Any T, N0, M1a, G2/G3
  - Any T, N1, M1a, any G
  - Any T, N2, M1a, any G
- **Stage IVc** any T, any N, M1b, any G
## Survival

<table>
<thead>
<tr>
<th></th>
<th>Mucinous</th>
<th>Adeno</th>
<th>Carcinoid</th>
<th>Goblet</th>
<th>Signet</th>
</tr>
</thead>
<tbody>
<tr>
<td>All stages</td>
<td>46</td>
<td>42</td>
<td>83&lt;sup&gt;a&lt;/sup&gt;</td>
<td>76&lt;sup&gt;a&lt;/sup&gt;</td>
<td>18&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Localized</td>
<td>64</td>
<td>64</td>
<td>94&lt;sup&gt;a&lt;/sup&gt;</td>
<td>86&lt;sup&gt;a&lt;/sup&gt;</td>
<td>55</td>
</tr>
<tr>
<td>Regional</td>
<td>54&lt;sup&gt;b&lt;/sup&gt;</td>
<td>37</td>
<td>83&lt;sup&gt;a&lt;/sup&gt;</td>
<td>74&lt;sup&gt;a&lt;/sup&gt;</td>
<td>21</td>
</tr>
<tr>
<td>Distant</td>
<td>32&lt;sup&gt;a&lt;/sup&gt;</td>
<td>11</td>
<td>31&lt;sup&gt;b&lt;/sup&gt;</td>
<td>18&lt;sup&gt;b&lt;/sup&gt;</td>
<td>7</td>
</tr>
</tbody>
</table>

Data are percentages.

*<sup>a</sup>*P < 0.0001 compared with adenocarcinoma five-year survival.

*<sup>b</sup>*P < 0.05 compared with adenocarcinoma five-year survival.

Appendiceal Tumor

Carcinoid
- <1cm
- 1-2cm
- >2cm
  - Appendectomy

Goblet Cell Carcinoid
- Mucinous adenocarcinoma
- Colonic type adenocarcinoma
- Signet ring cell adenocarcinoma
  - Right Hemicolecotomy
Appendiceal tumors are rarely diagnosed preoperatively.

Most present as acute appendicitis, followed by chronic abdominal pain or RLQ mass.

Carcinoid tumors < 1cm in size may be managed with appendectomy alone.

All others should be managed with right hemicolecotomy.

Two stage surgery is an acceptable approach to management of appendiceal tumors.

Carcinoid tumors have the best prognosis while adenocarcinoma (signet ring cell type) has the worst prognosis.
References

Carcinoid tumors

- 67% of all carcinoid tumors found in GI tract
- 25% found in tracheobronchopulmonary complex (most common extradigestive site), other sites: ovaries, testes, liver, GB, pancreas
- Within GI tract
  - 42% in small bowel, half in ileum
  - 27% rectum
  - 24% appendix
- Goodwin 1973 – gold standard paper – showed appendix most common – not true anymore
- Overall incidence 38.4/million