Navigating the Nomenclature of Appendiceal Mucinous Neoplasms

Rhonda K. Yantiss, M.D.
Professor of Pathology and Laboratory Medicine
Weill Cornell Medical College, New York, NY

Overview

- Pseudomyxoma peritonei
  - Definitions and grading
- Mucinous tumors of the appendix
  - Adenoma, LAMN, and carcinoma
- Mucin limited to the right lower quadrant
- Mimics of mucinous neoplasia

Clinical History

- 44 year-old male with right lower quadrant pain and suspected appendicitis
- Imaging revealed thickened appendix and fluid in right colic gutter
- Laparoscopic appendectomy and biopsies of peritoneum
Appendix

Diagnostic Options

- Mucin and neoplastic epithelium in peritoneum and appendix
  - Pseudomyxoma peritonei
  - Ruptured adenoma or cystadenoma of the appendix
  - Disseminated peritoneal adenomucinosis
  - Low-grade appendiceal mucinous neoplasm (LAMN)
  - Low-grade mucinous carcinoma peritonei

Appendiceal mucinous neoplasm
Peritoneal dissemination (pseudomyxoma peritonei)
Appendiceal mucinous neoplasm

Peritoneal dissemination (pseudomyxoma peritonei)

**Appendiceal mucinous neoplasm**

**Peritoneal dissemination (pseudomyxoma peritonei)**

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**Pseudomyxoma Peritonei**

*Controversial Issues*

- Definition
- Origin of epithelium (appendix, ovary, or peritoneum)
- Classification of mucinous neoplasms

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**Pseudomyxoma Peritonei**

*Variable Definitions*

- Mucin in the peritoneal cavity
- Some require epithelium, others do not
- Some include disease limited to right lower quadrant, others mean diffuse disease
- Some describe it associated with non-appendiceal tumors (e.g. colon cancer)
Epitheliu
m
Appendix
Primary
Ovary
Peritoneum

Origin of Pseudomyxoma Peritonei

<table>
<thead>
<tr>
<th>Grade/Disease</th>
<th>Epithelial</th>
<th>Appendix</th>
<th>Ovary</th>
<th>Peritoneum</th>
<th>Lymph Node Metastases</th>
<th>5-Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-grade diffuse peritoneal adenomucinosis (DPAM)</td>
<td>Scant</td>
<td>40%</td>
<td>12%</td>
<td>3%</td>
<td>84%</td>
<td></td>
</tr>
<tr>
<td>Intermediate-grade</td>
<td>Mixed</td>
<td>79%</td>
<td>79%</td>
<td>21%</td>
<td>38%</td>
<td></td>
</tr>
<tr>
<td>High-grade disease/peritoneal mucinous carcinomatosis (PMCA)*</td>
<td>Abundant</td>
<td>40%</td>
<td>97%</td>
<td>50%</td>
<td>7%</td>
<td></td>
</tr>
</tbody>
</table>

*40% of cases derived from colonic primary

Should not use "pseudomyxoma peritonei" as a diagnostic (pathologic) term since it means different things to different people

Appendix

Ovary

Peritoneum

Virtually all cases due to appendiceal primaries

Natural History of Pseudomyxoma Peritonei
Low-Grade Pseudomyxoma Peritonei

Invasive tumor cells at advancing front

Low-Grade Pseudomyxoma Peritonei

High-Grade Pseudomyxoma Peritonei
High-Grade Pseudomyxoma Peritonei

Infiltrating malignant cells with desmoplasia

Classification of Pseudomyxoma Peritonei

<table>
<thead>
<tr>
<th>Low Grade Epithelium in Peritoneum</th>
<th>High Grade Epithelium in Peritoneum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ronnett, et al.</td>
<td>Peritoneal mucinous adenocarcinoma</td>
</tr>
<tr>
<td>Misrahi, et al.</td>
<td>Invasive mucinous adenocarcinoma</td>
</tr>
<tr>
<td>Pai and Lunsford</td>
<td>Low-grade appendiceal mucinous neoplasm</td>
</tr>
<tr>
<td>Carr and Sobin (AFIP)</td>
<td>Invasive mucinous adenocarcinoma</td>
</tr>
<tr>
<td>Bradley, et al.</td>
<td>Invasive mucinous adenocarcinoma, low-grade</td>
</tr>
<tr>
<td>AJCC</td>
<td>Not specifically addressed, but staged as adenocarcinoma</td>
</tr>
</tbody>
</table>
International Peritoneal Surface Oncology Group Consensus
Basingstoke 2013 and Amsterdam 2014

- 60 pathologists, as well as surgeons and oncologists
- Delphic process (currently round 5)
  - Contentious questions
    - 2/3 majority agreement among non-abstainers and absolute majority of all participants
  - Non-contentious issues
    - Simple majority vote

Pseudomyxoma Peritonei
Clinical Definition
“Intraperitoneal accumulation of mucus due to mucinous neoplasia characterized by the redistribution phenomenon. It can include mucinous ascites, peritoneal implants, omental cake, and pseudomyxoma ovarii. It most commonly arises from appendiceal neoplasia.”

Peritoneal Surface Oncology Group Meeting
Amsterdam, Netherlands, October 2014.

Pseudomyxoma Peritonei
- Two-tiered grading system
- Grade of peritoneal disease assigned separately from the appendix
Mucinous Lesions Limited to the Appendix and Periappendix

Clinical History
- 54 year-old female with incidental appendectomy during gynecologic surgery
- Ovary contained a serous cystadenoma
- Appendix was grossly normal

Cross Section of Appendix
Cross Section of Appendix

Diagnostic Options
- Mucinous tumor of appendix confined to mucosa (or at least the inner appendix) with some high-grade areas
  - Mucinous adenoma/cystadenoma
  - Mucinous cystadenocarcinoma
  - Low-grade appendiceal mucinous neoplasm (LAMN)
  - High-grade appendiceal mucinous neoplasm (HAMN)?

Mucinous Adenoma
- Neoplasm limited to mucosa
- Epithelium often with villi or papillae
- Can be dilated due to mucin accumulation
  - “Cystadenoma”
  - Epithelium may be flat or undulating
- No much outside appendix
- Uniformly benign
Variably severe atypia
- Low-grade dysplasia
- High grade dysplasia
  - “Mucinous cystadenocarcinoma”
  - No risk of recurrence or metastasis
  - “Carcinoma” terminology best avoided

Preferred term: Adenoma

Caveats
- Some require intact muscularis mucosae and lamina propria
- May not be apparent in all cases
- Some require negative resection margin

Peritoneal Surface Oncology Group, Basingstoke 2013 and Amsterdam 2014

Mucinous Neoplasms Limited to Luminal Appendix

Low-grade appendiceal mucinous neoplasm?
Mucinous Neoplasms Limited to Luminal Appendix

Low-grade appendiceal mucinous neoplasm?
Obliterated lamina propria and/or muscularis mucosae common in appendices of patients with pseudomyxoma peritonei

- No data to suggest these findings are predictive of outcome in patients without peritoneal disease

Labeling tumors seemingly confined to mucosa as “low-grade appendiceal mucinous neoplasm” places patients in risk category that is likely unwarranted

Mucinous Neoplasms Limited to Appendiceal Mucosa

- Caveats
  - Some require intact muscularis mucosae
  - Some require negative resection margin
    - Mucinous tumor of uncertain malignant potential

Mucinous Adenoma

- No data to suggest that mucinous neoplasia in the mucosa (i.e. adenoma) at the margin poses biologic risk

- No data to suggest that mural acellular mucin at the margin poses risk (if all extra-appendiceal mucin is acellular)

- Neoplastic epithelium in the wall is a different story, but then we would not be considering adenoma as a possibility
**Mucinous Appendiceal Tumors**

- Tumors in peritoneum are essentially cancers
  - Behavior dependent on cytologic grade
    - Low-grade: 60% 10-year survival
    - High-grade: 10% 10-year survival
- Lesions limited to mucosa are benign, regardless of cytologic atypia
  - Mucinous adenoma (although others classify all mucinous tumors as low-grade appendiceal mucinous neoplasms)
  - Cystadenoma is no longer preferred terminology
- What about the “in between” cases?

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**Criteria for Diagnosis**

*Low-Grade Appendiceal Mucinous Neoplasm*

- Grossly similar to adenoma, but may see mucin on serosa
- Pushing invasion characterized by destruction of muscularis mucosae, fibrosis, herniations, dissecting mucin
- Equivalent to low-grade carcinoma and may recur in peritoneum
  - Risk higher if mucin is outside appendix and highest if mucinous epithelium is outside appendix
Case History

- 42 year old male with acute right lower quadrant pain
- CT revealed appendicitis with probable inflammatory mass
- Laparoscopic appendectomy
  - Inflammation without mucin on appendix or in abdomen

Cross Section of Appendix

Appendiceal Lumen
Appendiceal Wall

Mesoappendix

Appendiceal Wall
Diagnostic Options

- Mucinous tumor of appendix with mucin in wall and mesoappendix; not clear whether there is mural epithelium as well
  - Mucinous adenoma
  - Mucinous tumor of uncertain malignant potential
  - Low-grade appendiceal mucinous neoplasm (LAMN)
  - Low-grade mucinous adenocarcinoma

Considerations

- Abundant mural mucin with epithelium precludes diagnosis of adenoma
- Mucinous tumor of uncertain malignant potential
- Low-grade appendiceal mucinous neoplasm (LAMN)
- Low-grade mucinous adenocarcinoma

Follow-Up

- Patient developed mucinous ascites at 3 years
- Progressive disease despite multiple surgical procedures, intraperitoneal and systemic chemotherapy
- Essentially receiving hospice care at this point
Clinical History

- Young adult male with right lower quadrant pain and presumed appendicitis
- Laparoscopic examination
  - Distended appendix with injected serosa

Cross Section of Appendix

Cross Section of Appendix
Mucin and Epithelium Beyond Muscularis Mucosae, but Limited to Appendiceal Wall

Pushing Invasion?

Cross Section of Appendix

Diagnostic Options

- Mucinous tumor with neoplastic epithelium and mucin in wall
  - Mucinous adenoma
  - Mucinous tumor of uncertain malignant potential
  - Low-grade appendiceal mucinous neoplasm (LAMN)
  - Low-grade mucinous adenocarcinoma
Mucin and/or Epithelium Beyond Muscularis Mucosae, but Limited to Appendiceal Wall

- Not specifically addressed by most classification systems
- No data in literature regarding biologic risk of mural disease alone
- Regarded as carcinoma for AJCC staging purposes

Clinical History

- 44 year-old woman presented with seven months of abdominal symptoms
  - Bloating and abdominal fullness
  - Abdominal pain and nausea
- CT scan
  - Dilated fluid-filled appendix
  - Thickened, enhancing appendiceal wall
  - Pelvic fluid

Cross Section of Appendix
**Diagnostic Options**

- Mucinous tumor of appendix with neoplastic epithelium and mucin around the appendix, but not beyond right lower quadrant
  - Low-grade appendiceal mucinous neoplasm (LAMN)
  - Mucinous tumor of uncertain malignant potential
  - Low-grade mucinous adenocarcinoma

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**Disease Outside Appendix, Limited to Right Lower Quadrant**

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**Extra-Appendiceal Mucin Confined to Right Lower Quadrant**

No epithelium in mucin

Epithelial cells in mucin
**Extra-Appendiceal Mucin**

- Any epithelium outside appendix
  - Approximately 1/3 of patients develop pseudomyxoma peritonei
- No epithelium in extra-appendiceal mucin
  - Essentially cured by appendectomy
  - Caveats
    - Rare cases of recurrence, despite lack of detectable epithelium
    - Submit all of peri-appendiceal mucin


**Extra-Appendiceal Mucin Limited to Right Lower Quadrant**

- Any epithelium beyond muscularis mucosae
  - Low-grade mucinous carcinoma
  - Low-grade appendiceal mucinous neoplasm
- No epithelium beyond muscularis mucosae
  - Low-grade appendiceal mucinous neoplasm
  - Mucinous cystadenoma with extra-appendiceal mucin (rupture) and comment
    - Most lesions with these features are cured by excision alone, although rare cases may recur despite an absence of extra-appendiceal neoplastic epithelium (tumor cells). Clinical follow-up may be considered, if indicated.

**Classification of Appendiceal Mucinous Neoplasms**

<table>
<thead>
<tr>
<th>Pathologic Features</th>
<th>Diagnostic Options</th>
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<tbody>
<tr>
<td>Non-invasive tumor</td>
<td>Adenoma Low-grade appendiceal mucinous neoplasm</td>
</tr>
<tr>
<td>Non-invasive tumor</td>
<td>Adenoma High-grade appendiceal mucinous neoplasm</td>
</tr>
<tr>
<td>Infiltrative invasion, regardless of stage</td>
<td>Invasive adenocarcinoma</td>
</tr>
<tr>
<td>Desmoplasia may, or may not be present</td>
<td>Invasive adenocarcinoma</td>
</tr>
</tbody>
</table>
Appendiceal Mucinous Neoplasms
AJCC 7th Edition Staging Criteria

- Grade of epithelium beyond appendiceal mucosa
  - Low-grade mucinous carcinoma
  - High-grade mucinous carcinoma
- Tumor stage
  - T1: Tumor involves submucosa
  - T2: Tumor invades muscularis propria
  - T3: Tumor invades subserosa or mesoappendix
  - T4a: Tumor penetrates serosa, including tumor in the right lower quadrant
- Distant metastases
  - M1a: Intraperitoneal metastases beyond right lower quadrant
  - M1b: Extra-peritoneal metastases

Does Mucin Around Appendix Always Imply the Presence of a Neoplasm?

Clinical History

- 12 year old male with acute right lower quadrant pain and presumed appendicitis
- Laparoscopic appendectomy
- Appendix inflamed without perforation
Cell Clusters in Serosal Mucin Pools

Diagnostic Options
- Low-grade mucinous adenocarcinoma
- Low-grade appendiceal mucinous neoplasm (LAMN)
- Mucinous adenoma
- Ruptured diverticulum/post-inflammatory (non-neoplastic)

Appendiceal Mucosa
Mucin Pools

Cell Clusters in Serosal Mucin Pools

Mimics of Mucinous Neoplasia

Diverticulosis
Mimics of Mucinous Neoplasia

*Diverticulosis*

- Mucosal component is not neoplastic
- Extra-appendiceal mucin
  - Scant
  - Localized or circumscribed
  - Associated with apparent diverticula (also lined by non-neoplastic epithelium)
- Predominant features in appendix are inflammatory
Diverticulosis and Mucinous Neoplasia

Muscularis mucosae
Muscularis propria
Lamina propria
Localized extra-appendiceal epithelium

Diverticulosis Involved by Mucinous Neoplasia vs. “Pushing” Invasion

?Low-grade appendiceal mucinous neoplasm
Appendiceal Mucinous Neoplasms

Summary and Conclusions

- Uniform group of tumors with predictable course dependent on stage and grade
  - Mucosal neoplasia pursues benign course
    - Adenoma (may be called LAMN in future)
  - Neoplastic epithelium beyond muscularis mucosae may behave aggressively in stage dependent fashion
- Peritoneal disease increasingly recognized as a malignancy (mucinous carcinoma peritonei)
- Equivocal terminology (e.g. low-grade appendiceal mucinous neoplasm) should be reserved for specific situations in which biologic potential is unclear