Beyond Acute Appendicitis: Fascinating Lesions of the Vermiform Appendix

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The Appendix: historical perspectives

• Probably first noted by Egyptians around 3000 B.C.
• First sketched by da Vinci around 1500
  – Used term “orecchio,” or “ear,” to describe
• Formally described by da Capri (1521) and Vesalius (1543)

The Appendix: historical perspectives

• Phillippe Verheyen, a Belgian anatomist/surgeon, coined the term “appendix vermiformis” in 1710.

The Misunderstood Appendix
Wikipedia-quoting The Story of Evolution

• “The vermiform appendage-in which some recent medical writers have vainly endeavored to find a utility-is the shrunken remainder of a large and normal intestine of a remote ancestor.”
“Its major importance would appear to be financial support of the surgical profession.”

-Alfred Sherwood Romer and Thomas S. Parsons

“The Vertebrate Body” (1986)

The Misunderstood Appendix
The Naked Scientists’ Forum

“What does the appendix do? Lots of people have them removed in operations and don’t seem to miss it.”

“The appendix is a supplementary explanatory section at the end of books. I don’t know why people have them removed.”

The Misunderstood Appendix

“Instead of regarding the appendix as a vestigial organ, useless to man and not worthy of close attention by pathologists, it would perhaps be more useful to view the appendix as a miniature of the colon, reflecting the spectrum of pathology seen in the large bowel together with several organ-specific conditions which are of undoubted interest.”

-Williams and Myers, *Pathology of the Appendix*

The First Appendectomy

- Performed by Claudius Amyand, surgeon to King George II, December 6, 1735, at St. George’s Hospital in London
  - “Not a man of genius, but one of solid worth”
- Patient was Hanvil Anderson, age 11
- Presented with inguinal hernia and fecal fistula tract draining in the groin
The First Appendectomy

• No anesthesia
  – “Tis easy to conceive that this operation was as painful to the patient as laborious to me.”
    • Philosophical Transactions of the Royal Society, 1736
• Perforated appendix was found within a hernia sac (Amyand’s hernia)
• Supposedly caused by ingested pin that lodged in the appendix

Most Famous Appendectomy

• Prince Edward VII, son of Queen Victoria
• Became ill two weeks before coronation in 1902
• Treves finally convinced him to undergo the operation, which lasted less than an hour and was successful

Handling of Appendectomy Specimens

• General guidelines:
  – Measurements
  – External examination
    • Hyperemia, exudate, perforation, mucin
  – Transverse sections of margin, midportion
  – Longitudinal section of tip (2 cm)
  – Section remainder and examine
    • Lesions, masses, fecaliths, foreign bodies

Handling of Appendectomy Specimens

• If grossly dilated and neoplasm suspected:
  – Take margin
  – Bisect longitudinally
  – Representative sections
    • Invasion, perforation, extra-appendiceal mucin
Inflammatory Processes in the Appendix

- Acute “nonspecific” appendicitis
  - Granulomatous appendicitis
  - ?Chronic appendicitis
- Infections of the appendix
  - Viral
  - Bacterial
  - Parasitic
- Miscellaneous lesions
  - Malakoplakia
  - Appendiceal diverticula
  - Tumors frequently associated with appendicitis

Acute “nonspecific” appendicitis

- Most common intra-abdominal surgical emergency
- Peak incidence 2nd-3rd decades
- Perforation more common in children and very elderly
- Tumors associated with appendicitis in older adults

Earliest changes: serosal dullness, injection of vessels

Increased serosal dullness and early hyperemia/exudate
Over time, increasing hyperemia develops.....

......and purulent exudate.

Edema and extension of the neutrophilic infiltrate across the muscularis mucosa into the submucosa
Gangrenous appendix with green-gray mural discoloration

Eventual progression to transmural neutrophilic inflammation and necrosis
Acute Appendicitis
“minimal diagnostic criteria”

– Remain controversial
– Two camps:
  • Those who require neutrophils in submucosa/muscularis propria
  • Those who accept mucosal ulceration/acute inflammation as enough for diagnosis

Is the latter enough to explain the patient’s symptoms?

Acute Appendicitis
“minimal diagnostic criteria”

– Williams and Myers study
  • More than 1000 appendectomies
  • Detailed correlation of clinical, surgical, and pathological information
  • Found that mucosal neutrophilic infiltrates (usually with cryptitis or ulceration) represented the early stage of acute suppurative appendicitis, and that more sections usually led to finding neutrophils in wall

The Centrist Resolution

• Patients with symptoms and signs of AA may show only mucosal/submucosal acute inflammation
• However, enteric infections and trauma from fecaliths may produce similar histologic changes
• Therefore, “acute suppurative appendicitis” reserved for specimens with mural neutrophilic infiltrate
• Acute mucosal/submucosal appendicitis for those cases, with a comment
Campylobacter infection involving appendix

Acute Appendicitis-pathogenesis

- Rarely foreign bodies
- Obstruction
- Infection
- Vascular compromise
- No single theory can explain all cases
**Chronic Appendicitis**

- There are chronic appendiceal infections (e.g. tuberculosis)
- Some patients have recurrent AA before resection
- Appendix with scarring, plasmacytic infiltrate—probably resolving or ongoing AA
- Primary chronic appendicitis should not be used
- Luminal fibrosis with mild chronic inflammation is not chronic appendicitis

**The Negative Appendectomy**

- A certain percentage will be histologically normal, regardless of patient symptoms
- Submit the entire specimen
- Molecular and retrospective histologic studies inconclusive
- Symptoms usually still resolve after resection

**Selected Infectious Agents Affecting the Appendix**

<table>
<thead>
<tr>
<th>Parasites</th>
<th>Bacteria</th>
<th>Viruses</th>
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<tbody>
<tr>
<td>Pinworms</td>
<td>Yersinia</td>
<td>Adenovirus</td>
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<tr>
<td><em>Amoeba</em></td>
<td><em>Campylobacter</em></td>
<td>EBV</td>
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<tr>
<td>Schistosomes</td>
<td><em>Actinomyces</em></td>
<td>CMV</td>
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<tr>
<td><em>Strongyloides stercoralis</em></td>
<td>Tb/MOTT</td>
<td>Measles</td>
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<tr>
<td>Other helminths</td>
<td><em>Salmonella</em></td>
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<td></td>
<td><em>Shigella</em></td>
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**Adenovirus in the Appendix**

- Associated with ileal and cecal intussusception
- Most often in children
- Patients usually do not have signs and symptoms of acute appendicitis
Marked lymphoid hyperplasia in Adenovirus infection

Adenovirus immunostain highlights intra-epithelial inclusions

Warthin-Finkeldy giant cells in the appendix
Granulomatous Appendicitis

- Infection
  - *Yersinia*
  - Actinomycosis
  - Tb/MOTT
  - Parasites
- Interval appendectomy
- Sarcoidosis
  - Crohn’s disease less than 10% of the time

Yersinia Appendicitis

- Fastidious, Gram negative bacilli cause wide range of GI diseases
- Present in many food sources
- Invasive *Yersinia* (*enterocolitica* and *pseudotuberculosis*) responsible for about 25% of granulomatous appendicitis cases
- Usually self limited

Yersinia - Diagnosis

- DDx: Crohn’s, other infectious causes
- Not usually detectable with Gram stain or immunostains
- Diagnosis:
  - Culture (fastidious organism)
  - Serologies (false negatives)
  - PCR
  - High index of suspicion

Nodular mucosa overlying thickened wall
Lymphoid hyperplasia and epithelioid granulomas

Linear array of lymphoid aggregates mimics Crohn’s Disease
Granulomas with central microabscesses in *Y. pseudotuberculosis*

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**Actinomycosis: *Actinomyces israelii***

- Normal commensal
- Any level of GI tract
- Usually solitary mass, invading adjacent structures
  - Sometimes associated with diverticulosis
- **Symptoms:**
  - Acute appendicitis
  - Fever, abdominal pain
  - +/- palpable mass
• Gram, GMS, Steiner positive
• DDx:
  – *Nocardia* (partially acid fast)
  – Other bacteria that form clusters or chains, but are not truly filamentous, e.g. *Pseudomonas, E. coli*

Splendore-Hoepli Phenomenon
Enterobius vermicularis - Pinworms

- One of the most common human parasites
  - Most common appendiceal parasite
- Prevalent in developed countries
- Generally infect children and adolescents

“At any socioeconomic level, families with two or more children can expect at least one bout of enterobiasis.” - Leopairut et al, *Pathology of Infectious Diseases*

Pinworms
The appendicitis controversy

- Present in 0.6-13% of appendectomies
- Ability to actually cause mucosal damage and inflammation is hotly debated
- Some believe they invade peri-appendectomy
- Rarely observed to cause invasion, ulceration, inflammation in appendix, colon, female genital tract, and peritoneum
• Can often appreciate intestine, uterus
• Eggs are ovoid with one flat side, two layered refractile shell
Appendiceal Malakoplakia

- Malakoplakia
  - "malakos" = soft
  - "plakion" = plaque
- Rare granulomatous disease of uncertain etiology
- Originally described in 1902 (Michaelis & Gutmann)

Appendiceal Malakoplakia

- Sometimes associated with colorectal adenocarcinoma
- Many patients have underlying immunocompromise
- Soft yellow-tan plaques or masses may infiltrate wall or nodes
- May cause bleeding, obstruction, diarrhea, mass

Appendiceal Malakoplakia Pathogenesis

- ? Occult bacterial infection
- Intracellular bacteria on EM
- M-G bodies: bacterial capsule
- Numerous recovered organisms:
  - *E. coli*, *Klebsiella*, *Aeromonas*, *Rhodacoccus*, *Yersinia*
Appendiceal Diverticula

- 10% congenital, 90% acquired
- Acquired diverticula present in 0.4 - 2% appendectomies
- Probably underreported
- Associated with numerous conditions:
  - Neoplastic epithelial lesions
  - Neuromas
  - Cystic fibrosis

Appendiceal Diverticula
Pathogenesis

- Postinflammatory weakening of wall
- Anatomic weakness in the appendiceal wall (similar to colonic diverticula)
- Resulting from lumenal obstruction

Special stains negative; M-G bodies iron and calcium positive
Appendiceal Diverticula

- Single or multiple
- Often less than 5mm
- On mesenteric or antimesenteric border
- 25% at tip
Appendiceal Neoplasms Often Presenting with Acute Appendicitis

- Neuromas
- Goblet cell carcinoids
- Appendiceal mucinous tumors

Appendiceal Neuromas

- “Neuroappendicopathies” first recognized by Masson in the 1920s
- Controversial, incompletely understood relationship between neuromas and
  - appendicitis-like symptoms
  - fibrous obliteration; ?post inflammatory
  - development of carcinoid tumors
- "Lack of recognition of appendiceal neuromas remains the largest obstacle to determining the place of these proliferations in the genesis of disease processes and symptoms." - Richard Williams, *Pathology of the Appendix*

Appendiceal Neuromas

- Incidence up to 25% in some series
- +/- discrete mass
- Always at tip, submucosal
- Tan-pink cut surface

Loose proliferation of spindle cells in myxoid or fibroadipose background
Eosinophils are very common; mast cells variably present.

Appendiceal Neuromas
- S100 and NSE positive
- CD-117 negative

Appendiceal Carcinoids
- Most common location of classical carcinoid in gastrointestinal tract

Carcinoid, classical type
Carcinoid Variants Exclusive to the Appendix

- Tubular carcinoids
- Goblet cell carcinoids

Tubular Carcinoids

- Carcinoid variant virtually exclusive to appendix
- Generally asymptomatic, incidental findings

Small, uniform groups of cells forming tubular or linear structures, with prominent stroma
Neuroendocrine cells are typical; goblet cells rare
Tubular Carcinoid
Histology

- IHC:
  - CEA, cytokeratin, glucagon +
  - Other neuroendocrine markers variably +

Tubular Carcinoid
Clinical Importance

- DDx: lobular breast cancer
- Compared to goblet cell carcinoid:
  - Better prognosis
  - Clinically, behave similarly to classical appendiceal carcinoids
  - Metastasis rare
  - Hemicolecotomy not necessary

Goblet Cell Carcinoids

- Described in French literature in 1969
- Since then, many different names coined:
  - Crypt cell carcinoma, mucinous carcinoid, microglandular carcinoma, adenocarcinoid
  - “It is intriguing when as few as 150 reported cases of anything result in 5 different names.” - Henry Appelman
- 6th decade
- Equal gender distribution
- May present as acute appendicitis
- Like other types of carcinoid, often an incidental finding
**Goblet Cell Carcinoid**

**Histology**

- Neuroendocrine markers, CEA, cytokeratin +
- Glucagon usually negative

Goblet cell carcinoid—note tight clusters and basally located nuclei

- Infiltration of wall by groups of goblet cells in clusters or strands
- Cytoplasm is mucin +
- May have rare Paneth cells
**Goblet Cell Carcinoid**

**Clinical Implications**

- Probably more closely related to adenocarcinomas than carcinoids
- Should be expected to behave like low grade adenocarcinomas
  - Prognosis worse than classical carcinoid
  - Metastasis/recurrence common
  - Hemicolecotomy surgical treatment of choice

**Adenocarcinoma ex GCC**

- Signet ring cell adenocarcinoma
  - Discohesive infiltrating signet ring cells
  - Lack of cohesive goblet cell clusters
  - Significant cytologic atypia
  - Destruction of appendiceal wall
  - 38% stage-IV matched disease free survival
- Poorly differentiated adenocarcinoma
  - Glands, sheets of cells, high grade undifferentiated component
  - 0% stage-IV matched disease free survival
Goblet cell carcinoid vs. de novo signet ring cell adenocarcinoma

- Many single signet ring cells
- No goblet cell carcinoid morphologic component
- Don’t express neuroendocrine markers

Low Grade Appendiceal Mucinous Neoplasms

- Low grade appendiceal mucinous tumors are a difficult area of surgical pathology
- “Lesions that cause death through widespread intra-abdominal disease may be extremely well differentiated, exhibit pushing edges rather than infiltration, and lack desmoplasia.” - Carr and Sobin
LAMN
Clinical features

- 6-7th decade
- Associated with synchronous/metachronous colorectal adenocarcinoma
- Present as:
  - Acute appendicitis
  - Mass
  - Signs of peritoneal spread
  - Incidental finding

- Enlarged, >2 cm appendix
- Dilated wall, often associated mucocele
- +/- mucin on appendiceal surface

Pushing border without desmoplasia
Atrophic wall with lymphoid aggregates

LAMN
Controversies in Terminology and Diagnosis

- Various names
  - Adenoma, cystadenoma, mucocele, MTUMP, MTLMP, adenocarcinoma, cystadenocarcinoma
- Problems with diagnosis of invasion:
  - Muscularis mucosa often replaced by fibrosis
  - Presence of diverticula
- Extremely low grade tumors can cause intra-abdominal spread and death
Appendiceal Mucinous Neoplasms
A Clinically Useful Classification

• **LAMN:**
  – Dilated appendix; may have extra-appendiceal mucin grossly, +/- rupture
  – Low grade mucinous epithelium
  – No architectural complexity or high grade nuclei
  – Thinning of wall, atrophy of lymphoid tissue
  – Associated with diverticula
  – May have mural mucin, but no cells
  – May have peritoneal spread

  Misdraji et al, AJSP 27:1089-1103, 2003

• **Mucinous adenocarcinoma:**
  – Dilated appendix, variable extra-appendiceal mucin, rupture
  – More likely to have identifiable invasion/infiltrative growth pattern
  – Marked cytologic atypia
  – Architectural complexity
  – Dissecting mucin with atypical cells
  – May have peritoneal spread

  Misdraji et al, AJSP 27:1089-1103, 2003

LAMN vs. MACA

• Rigorous sampling required
• LAMN cannot have high grade nuclei, architectural complexity, or invasion
• Both LAMN and MACA may have peritoneal spread; grade of epithelium should be specified
  – Prognostic significance
  – The rare LAMN with high grade peritoneal epithelial elements behaves as MACA
Outcomes

- MACAs have significantly decreased survival over LAMN
- LAMN with peritoneal spread (low grade epithelial elements) still have better survival than MACA

Therapeutic Implications

- If no extra-appendiceal disease, and negative margins, appendectomy is curative
- If peritoneal disease is present, debulking may be of value
- Some MACA patients may also be offered chemotherapy
- Be sure of primary site

THANK YOU!