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)

Anatomy/Histology

- Same basic structure as the colon with a few exceptions:
  - Muscular wall development more irregular
  - Muscularis mucosae may be discontinuous
  - Prominent lymphoid tissue
  - Abundant ganglion cells and neuroendocrine cells
Anatomy/Histology

• Age-related changes
  – Is largest in childhood (maximum diameter age 4); shrinks throughout adult life
  – Lymphoid tissue diminishes after age 25
  – Fibrous tissue increases (especially after age 40)

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

• 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

Acute Appendicitis-pathogenesis

- Rarely foreign bodies
- Obstruction
- Infection
- Vascular compromise
- No single theory can explain all cases
Earliest changes: serosal dullness, injection of vessels

increased serosal dullness and early hyperemia/exudate

Over time, increasing hyperemia develops.
Edema and extension of the neutrophilic infiltrate across the muscularis mucosa into the submucosa.

......and purulent exudate.
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?
Solution 1-More Sections

– 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

Solution 2-The Centrist Resolution (Carr et al)

• 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 Nonspecific Appendicitis
Differential Diagnosis

- Periappendicitis/extra-appendiceal cause of inflammation
  - Pelvic inflammatory disease
  - Other intra-abdominal disease processes
- Infection
- Vasculitis
Acute Nonspecific Appendicitis
Differential Diagnosis

- Appendiceal diverticula
- Chronic idiopathic inflammatory bowel disease
  - Ulcerative colitis
    - Usually contiguous from cecum
    - May have appendiceal "patch"
  - Crohn’s disease
    - 40% of patients with ileocecal disease have appendiceal involvement
I think my caterpillar has appendicitis.

What about “chronic appendicitis?”

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

Interval appendectomy
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
Appendix-Viral Infections

- Adenovirus
- Measles
  - May precede prodrome and rash
- CMV
  - Almost always AIDS patients
- Epstein-Barr virus
  - Usually in context of mononucleosis

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
Adenovirus immunostain highlights intra-epithelial inclusions
Appendix-Bacterial Infections

- *Yersinia* species
- *Actinomyces israelii*
- Tuberculosis
- Enteric infections from colon
  - Rare; *Salmonella, Shigella, Campylobacter*
- *C. difficile*
Yersinia Appendicitis

- Gram negative bacilli cause wide range of GI diseases
- Present in many food sources
- *Yersinia (enterocolitica and pseudotuberculosis)* responsible for about 25% of granulomatous appendicitis Usually self limited
- Diagnosis:
  - PCR and high index of suspicion
  - Culture and serologies less useful

Nodular mucosa overlying thickened wall

Lymphoid hyperplasia and epithelioid granulomas
Crohn’s disease is main entity in differential diagnosis.

Isolated granulomatous appendicitis is Crohn’s disease less than 10% of the time.
Linear array of lymphoid aggregates mimics Crohn’s Disease

**Actinomycosis: Actinomyces israeili**

- 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
DDx:
Nocardia (partially acid fast)
Other bacteria that form clusters or chains, but are not truly filamentous, e.g. Pseudomonas, E. coli
Splendore-Hoeppli protein is helpful

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Gram positive and filamentous

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C. difficile
Appendix-Parasitic Infections

- *Enterobius vermicularis* (pinworm)
- *Strongyloides stercoralis*
- Schistosomiasis
- *Cryptosporidium*
- Roundworms (*Ascaris*)
- Whipworms (*Trichuris*)

*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
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

- Single or multiple
- Often less than 5mm
- On mesenteric or antimesenteric border
- 25% at tip
They say you are what you eat. But no one gave me a hot dog to wear this stupid outfit.

Appendiceal Neoplasms Often Found Incidentally

- Neuromas
- Well differentiated neuroendocrine tumors (carcinoids)
Incidence up to 25% in some series
+/- discrete mass
Always at tip, submucosal

Eosinophils are very common; mast cells variably present

**Appendiceal WNET**

- Most common location in gastrointestinal tract
L-cell WNET (tubular carcinoid)

- Virtually exclusive to appendix
- IHC:
  - CEA, cytokeratin, glucagon +
  - May express CK7 and/or CK20
  - Other neuroendocrine markers variably +
L-cell WNET (tubular carcinoid)

- DDx: lobular breast cancer
- Clinically, behave similarly to EC-cell WNET
  - Metastasis rare
  - Hemicolecotmy usually not necessary

Appendiceal Neoplasms Associated with Acute Appendicitis

- Goblet cell carcinoids
- Appendiceal mucinous tumors

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
Goblet Cell Carcinoid
Histology

- Cytokeratin positive
- Neuroendocrine markers variably positive

Goblet cell carcinoid–note tight clusters and basally located nuclei
Goblet Cell Carcinoid
Clinical Implications

• Should be expected to behave like low grade adenocarcinomas
  – Prognosis worse than WNET
  – Metastasis/recurrence common
  – Hemicolectomy surgical treatment of choice, often with lymph node dissection
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
  – Very poor prognosis

• Poorly differentiated adenocarcinoma
  – Glands, sheets of cells, high grade undifferentiated component
  – Even worse prognosis
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 tumors
Challenges in Terminology and Diagnosis

• Extremely low grade tumors can cause intra-abdominal spread and death

• Problems with diagnosis of invasion:
  – Muscularis mucosa often replaced by fibrosis
  – Presence of diverticula

It's hard to know what to call something that is very low grade and noninvasive but can kill you

LAMN vs. Cystadenoma

• Cystic dilatation
• Low grade epithelium
• Disruption of muscularis mucosae
• Mural atrophy/fibrosis
• Mural or extraappendiceal mucin

• Cystic dilatation
• Low grade epithelium
• Intact muscularis mucosae
• No mural mucin or extraappendiceal mucin

• Enlarged, >2 cm appendix
• Dilated wall, often associated mucocele
• +/- mucin on appendiceal surface
Pushing border without desmoplasia

Atrophic wall with lymphoid aggregates
When to diagnose invasive low grade adenocarcinoma

- When there is true invasion
- When there is cellular mucin outside of the appendix
  - Some people still call this LAMN with extracellular mucin outside the appendix
  - Need to submit all the tumor and mucin
Outcomes

- Acellular mucin in RLQ: low risk of progression
- 1/3 of patients with any amount of cellular mucin outside of the appendix progress to peritoneal disease
- Low grade mucinous adenocarcinoma with peritoneal disease has 5yr survival rate of 75%
- AJCC 8th edition is changing the staging of LAMN significantly
Therapeutic Implications

- If no confined to appendix with negative margins, appendectomy curative
- If acellular mucin outside of appendix, follow, but no evidence that further surgery/chemo has benefit
- Controversial for patients with cellular peritoneal mucin
  - Debulking
  - +/- intraperitoneal chemotherapy

THANK YOU!