Infections of the Esophagus and Small Intestine

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A Practical Approach

Esophagus
• Esophagitis
  ▪ DDx
  ▪ Common infectious causes
• Uncommon infections

A Practical Approach

Small bowel
• Pattern of injury
  ▪ “Normal”
  ▪ Inflammation
  ▪ Lamina propria expansion
  ▪ Eosinophils
• Specific organisms
  (Neoplasms)
Infections of the Esophagus

Esophageal Biopsy

- **Acute Esophagitis**
  - GERD
  - Infection:
    - Candida
    - CMV
    - HSV
  - Pills

- **Lymphocytes**
  - GERD
  - Lymphocytic esophagitis
  - Infection:
    - Candida

- **Granulomas**
  - Crohn Disease
  - Sarcoidosis
  - Infections unlikely:
    - Mycobacterial
    - Fungal

Esophagitis

- GERD – most common cause of "esophagitis"
  - Erosive and Non-erosive
  - Variable mixture of lymphocytes, neutrophils and eosinophils
  - Reactive features
    - Basal cell hyperplasia
    - Elongated papillae
    - "Ballooning" squamous cells
    - Edema
**Esophagitis**

*Always need to look for infectious cause of inflammation*

- Esp if there are neutrophils
- Once the biopsy is deemed negative for infection, it is probably GERD

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**Esophagitis**

- Infectious esophagitis usually occurs in the immunocompromised
  - Predisposing factors: antibiotic use, radiation therapy or chemotherapy, hematologic malignancies, AIDS, diabetes
- Symptoms: Dysphagia and odynophagia
- Diagnosis: Biopsies should sample both the ulcer bed and edge of ulcer

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**Esophagitis: Candida**

- *Candida albicans* or *Candida tropicalis*
- Most common cause of infectious esophagitis*
- AIDS-defining condition in an HIV+ patient
- Endoscopic appearance

*Can infect other sites in the GI tract*
Esophagitis: Candida

- Acute inflammation
- Yeast and pseudohyphae 1st in sloughed exudate (will be positive on PASD and GMS stains)
- Pseudohyphae needed to Dx infection (vs colonization)

Esophagitis: HSV

- Herpes simplex or varicella-zoster virus
  - HSV type I is the most common cause
  - Remains latent in healthy individuals
- Acute onset of symptoms
- “Always” occurs in immunocompromised
- Infects squamous epithelial cells
  - Present at immediate edge of ulcer
  - Often within desquamated cells
Esophagitis: HSV

- Ground-glass nuclei
- Nuclear molding
- Cowdry A intranuclear viral inclusions
- Multinucleated giant cells

Esophagitis: CMV

- Cytomegalovirus
  - Herpesvirus family
  - Remains latent in healthy individuals
  - Usually gradual onset of symptoms
  - “Always” occurs in immunocompromised
  - Infects endothelial cells, stromal cells and macrophages (and glandular cells)
    - Present in the base of ulcer or in inflamed subepithelial / granulation tissue
    - Does not infect squamous cells
Esophagitis: CMV

Similar endoscopic/gross appearance as HSV

Candida, HSV and CMV can occur in same patient

* So don’t stop looking once one infection is identified!*
Esophagus: Uncommon Infections

Chagas disease
- Caused by the parasite *Trypanosoma cruzi*
- More common in Latin America than in US
- After acute infection, organisms become latent
  - Up to 10% with chronic infection develop esophageal disorders; 3% develop megaesophagus

Esophagus: Uncommon Infections

Chagas disease
- Chronic inflammation of the myenteric plexus with loss of ganglion cells
- Resultant narrowing of distal esophagus and widening of proximal esophagus (secondary cause of achalasia)

Infections of the Small Bowel
Small Bowel (Duodenal) Biopsy

- **Normal**
- **Peptic Duodenitis**
  - Infection: H. Pylori
  - Drugs (NSAIDs)
  - IBD
- **IELs with preserved architecture**
- **Inflamed “flat” mucosa**
  - Celiac Disease
  - IBD
  - Autoimmune enteropathy
  - Drugs

Small Bowel Infections

- **Symptoms:**
  - Diarrhea
  - Nausea, vomiting, bleeding, bloating, abdominal pain

Bacterial infections (enterocolitis) involving the small bowel are beyond the scope of this lecture. Not covered:
  - Typhoid (Enteric) Fever [affects TI]
  - Yersinia [affects TI]
Infectious Agents - Protozoa

- Flagellates:
  - *Giardia lamblia*:
    - Common parasitic (protozoal) infection (not just the immunocompromised)
    - Explosive, foul-smelling diarrhea
    - Contaminated water
  - *Leishmania donovani*:
    - Uncommon in US; GI involvement rare

- Coccidians:
  - *Cryptosporidia*
  - *Microsporidia*
  - *Cyclospora*
  - *Isospora*
  - Not just seen in HIV+

**Giardia**

- Reside on luminal surface
- Binucleate
- 4 flagella
**Cryptosporidia**
- Reside on luminal surface
- Any glandular mucosa
- 2 to 5-µm, round, basophilic
- Easily confused with mucin globules

**Microsporidia**
- Enterocytozoon bieneusi and Encephalitozoon intestinalis
- Patchy blunting and chronic inflammation
- Diarrhea and wasting
- Least likely to infect immunocompetent

**Microsporidia**
- Reside within epithelial cells
- 2 to 3-µm

(Photos courtesy of Dr. Rhonda Yantiss, Dept. of Pathology, Weill Cornell Medical College)
Microsporidia

- Reside within enterocytes
- 2 to 3-µm schizonts
- 5 to 6-µm banana-shaped merozoites
- May be asymptomatic
- Worldwide distribution

Cyclospora

- Reside within enterocytes
- 2 to 3-µm schizonts
- 5 to 6-µm banana-shaped merozoites
- May be asymptomatic
- Worldwide distribution

Isospora

- Causes mucosal inflammation and injury
- Infects epithelial cells and macrophages
- 15 to 20 µm
- Round and banana shapes
- Non-bloody diarrhea with crampy abdominal pain
- Peripheral eosinophilia
- Worldwide distribution but more common in tropics

Photo courtesy of Dr. Laura Lamps, Dept. of Pathology, University of Arkansas

From a case done by Dr. Rhonda Yontos, West Cornell Medical Center.

Courtesy of Dr. Joel M. Simmons, University of Buffalo.
Infectious Agents - Worms

- *Strongyloides stercoralis* (Nematode)
  - Diarrhea, abdominal pain, N/V, or asymptomatic; Rash, eosinophilia
  - Present within crypts
  - Associated mixed inflammation, villous blunting, ulcers

- *Schistosomiasis* (Trematodes)
  - Diarrhea (bloody), anemia, weight loss, and protein-losing enteropathy
  - Granulomatous inflammation often with eosinophils in polyps, ulcers; can mimic IBD

Photos courtesy of Dr. Doug Hartman, Dept. of Pathology, University of Pittsburgh
Schistosomiasis

Infectious Agents

**Mycobacteria**
- *Mycobacterium avium-intracellulare (MAI)*
  - Diarrhea, abdominal pain, fever, weight loss
  - Endoscopy often normal or shows small white patches
  - Infects histiocytes/macrophages
- *Mycobacterium tuberculosis (TB)* can also infect the GI tract, often the distal small bowel and cecum
Lamina propria expansion
Infectious Agents

Fungal Infections
- Primarily found in immunocompromised patients (but can be found in the immunocompetent)
- Often part of disseminated disease
- Symptoms: diarrhea, N&V, melena, bleeding, abdominal pain, and fever
- Histology:
  - Suppurative, necrotic and/or granulomatous reaction
  - Fungal hyphae or spores can be highlighted with GMS and PASD stains

Fungal Infections – Filamentous Fungi
- Aspergillus species – uniform, septate hyphae; branch at acute angles
- Mucormycosis – broad, ribbon-like hyphae; rare septae; branch at any angle
- Basidiobolomycosis
  - Occur in children and patients with peptic ulcer disease, diabetes, pica, ranitidine use; not the immunocompromised
  - Increasing incidence in US (Arizona)
- Phaeohyphomycosis
  - Pigmented
Infectious Agents

Fungal Infections - *Basidiobolus ranarum*

- Eosinophilia, granulomas, Splendore-Hoeppli reaction
- Mucor-like, but "crinkled" (GMS)


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Infectious Agents

**Fungal Infections – Yeast**

- **Candida albicans, Candida tropicalis**
  - Can infect entire GI tract
  - Often infects / involves / causes ulcers
- **Cryptococcus neoformans**
  - 4-7 um, "halo" around organisms
- **Histoplasma capsulatum**
  - Lymphohistiocytic inflammation
  - Small (2-5um), narrow-budding

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Infectious Agents

**Fungal Infections – Yeast (Cont’d)**

- **Penicillium marneffei**
  - Small (2-5um), non-budding, infect histiocytes
  - Transverse septum; appears "pinched" in the middle
  - Suppurative and/or granulomatous reaction
- **Pneumocystis jiroveci**
  - Can infect the GI tract of immunocompromised (including patient on infliximab therapy for Crohn disease and rheumatoid arthritis)
Infectious Agents

Chronic infections

- Whipple's disease - *Tropheryma whipplei*
  - Affects predominantly men
  - Diarrhea, abdominal pain, weight loss, and joint pains and lymphadenopathy
  - Endoscopy: Thickened pale friable folds
  - Histology:
    - Expansion of lamina propria by grey-blue macrophages
    - Often have dilated lymphatics
    - PASD+ organisms within macrophages

Lamina propria expansion

Histoplasma capsulatum

(McCullough K, 2005)
Infectious Agents

Chronic infections

- Bacterial overgrowth
  - Coliform bacterial colonization of small bowel
  - Diarrhea, abdominal pain, and bloating → maldigestion and malabsorption
  - Postulated to be a cause of IBS
- Treatment/Diagnosis: Response to antibiotics
  (Quigley EM, 2014)
- Typically causes increased IELs with intact villous architecture
- Can be seen in SBO (proximal to obstruction) and in surgically created limbs, pouches
Infections of the Esophagus and Small Intestine

Summary
- Numerous types of microorganisms can infect the esophagus and small bowel
- Recognizing the pattern of injury helps identify the infectious agent
- Many, but not all, infections occur in the immunocompromised
- More than one infection can occur at the same time in the same specimen

Thank You!

Infection and Neoplasia
**Esophagus: Squamous papilloma**

- Anal squamous lesion: 1st thought = HPV
- Esophageal squamous lesion: 1st thought, not usually HPV

**Esophagus: Squamous papilloma**

- Usually solitary, asymptomatic and found in the distal esophagus
- Controversial etiology:
  - Human papilloma virus (86% HPV+ by PCR) (Bohn OL. 2008)
  - Chronic irritation (Only 4% HPV+) (Carr NJ. 1994)
  - Combination (50% HPV+ by PCR) (Odze R. 1993)

**Infection and Esophageal Malignancy**

- HPV: established association with cervical and oropharyngeal SCC
- 1st thought for esophageal SCC (in USA), not HPV
Infection and Esophageal Malignancy

- Esophageal SCC – association with HPV may be regional
  - Areas with low prevalence of SCC
    - North America: 2% HPV+ by PCR (Turner JR. 1997);
      10% HPV+ metanalysis (Syrjänen K. 2013)
    - Europe, 18% (Syrjänen K. 2013)
  - Areas with high prevalence of SCC
    - China, 42% (Syrjänen K. 2013)
- Likely causative in a limited # of SCC and primarily in high risk areas
- p16 is not a reliable marker of HPV status in esophageal SCC (Michaelsen SH. 2014)

Infection and Malignancy

- HHV8: Kaposi Sarcoma
  - 4 forms:
    - Classical variant (elderly men from Eastern Europe and Mediterranean countries)
    - Lymphadenopathy-associated (endemic or African form)
    - Transplant- or immunosuppression-associated
    - AIDS-associated (epidemic form):
      - Most common AIDS-associated tumor in the US
      - Most common GI malignancy in AIDS patients (Arora M. 2010)

Infection and Malignancy

- HHV8: Kaposi Sarcoma
  - Symptoms: weight loss, N/V, GI bleeding, diarrhea or asymptomatic
  - Endoscopy:
    - Purple maculopapular lesions (often multiple)
    - Large nodules and polypoid lesions
  - Histology: HHV8+
    - Spindle cells arrange in vague fascicle with slit-like spaces containing RBCs, HHV8+
    - Hyaline globules & moderate atypia can be seen
    - Vascular tumor: Positive for CD31, CD34, D2-40, and FLI1
Thank You!