Update on Infections in the Immunocompromised Host

Rodger C. Haggitt
Gastrointestinal Pathology Society
Sunday, March 18, 2012

Laura W. Lamps, M.D.
University of Arkansas for Medical Sciences
Little Rock, AR
What’s New: Infections in the Immunocompromised

- Emerging GI fungal infections
- Unusual atypical mycobacterial infections
- Update on pseudomembranous colitides
Who is immunocompromised?

- AIDS
- Chemotherapy
- Solid organ and bone marrow transplants
Who is immunocompromised?

- Elderly patients
- Young children
- Patients with IBD, autoimmune disease on chronic immunomodulator therapy
- Corticosteroid use
Who is immunocompromised?

- Diabetics
- Patients without spleens
- Chronic alcoholism
- Malnutrition
- Any chronic debilitating disease
Emerging Fungal Infections
Case Example

- A 75 year old debilitated, severely diabetic patient presented with upper GI bleeding. Endoscopy showed a large gastric ulcer. The ulcer had prominent rolled edges, and was macroscopically worrisome for malignancy. Biopsies were taken.
Mucormycosis

• Formerly known as zygomycosis
  – Order *Mucorales* has replaced *Zygomycetes*

• Risk factors:
  – Diabetes (or any metabolic acidosis)
  – Immunosuppression (but rare in AIDS)
  – Prematurity
  – Malnourishment
GI Mucormycosis

- Often caused by colonization of ulcers
- Stomach and colon are most frequently involved sites
- Ulcers often have heaped-up, rolled edges that mimic malignancy grossly
- Pathologic features very similar to aspergillosis
- Broad, ribbon-like, pauciseptate hyphae
- Random branching
- Optically clear on cross-section
- Angioinvasive
Case Example

- 41 year old man presented with abdominal pain and obstructive lower GI symptoms. Colonoscopic mucosal biopsies were normal. CT scan showed a large cecal mass. Laboratory tests were significant for peripheral eosinophilia.
Basidiobolomycosis

- *Basidiobolus ranarum*, closely related to Mucor
- Worldwide soil saprophyte
- Until recently, primarily considered a subcutaneous infection
- Most cases reported in Saudi Arabia, Africa, South America; current cohort of cases in Arizona
Basidiobolomycosis

- Susceptible populations:
  - Children
  - Peptic ulcer disease
  - Diabetes
  - Pica
  - Ranitidine use
  - Living in an endemic area
Gastrointestinal Basidiobolomycosis

- GI cases can mimic malignancy, idiopathic inflammatory bowel disease
- Pericolonic, perigastric fibroinflammatory mass with granulomatous inflammation
- Most cases respond to long-term antifungal therapy, but colonic perforation, dissemination, and death are well-documented
Gastrointestinal Basidiobolomycosis

- Histologic features:
  - Lack angioinvasion
  - Organisms are rare
  - Splendore-Hoeppli material
  - Necrosis, granulomas
  - Prominent eosinophils
  - Marked fibrosis
Case Example

• A 65 year old patient undergoing chemotherapy for multiple myeloma had sudden-onset GI bleeding. Endoscopy revealed multiple gastric and duodenal ulcers. Surgery was ultimately undertaken to control the bleeding.
Phaeohyphomycosis

- Dematiaceous (naturally pigmented) fungi
- Occurs worldwide in humans and animals
  - Saprophyte found in soil, wood, vegetable matter
  - Over 70 species
  - Usually infects immunocompromised patients, but can occur in healthy patients
Phaeohyphomycosis

- Most common sites of infection are subcutaneous, sinonasal
- Risk factors
  - Neutropenia/chemotherapy
  - Bone marrow/solid organ transplant
  - Farming, gardening, outdoor work
  - Well documented in immunocompetent individuals as well
Phaeohyphomycosis

- Fungi are darkly pigmented in tissue sections (H&E)
  - Speciation requires culture or PCR; not possible on morphologic grounds alone
- Inflammatory reaction may be granulomatous or suppurative
- Stain with GMS, PAS, melanin stains
Filamentous Fungi

- Broad ribbon-like hyphae, angioinvasion-? *Mucor*
  - Correlate with clinical history, cultures; Galactomannan and Beta(1.3) D glucan negative

- Uniform septate hyphae that branch at acute angles
  - *Aspergillus*
    - Cultures Galactomannan + Beta(1.3) D glucan +
  - *Fusarium*
    - Cultures Galactomannan – Beta(1.3)D glucan +

- Pigmented-? Phaeohyphomycosis
  - Cultures Molecular Galactomannan – Beta (1.3)D glucan +
Case Example

- A 25 year old Asian patient, HIV+, presented with diarrhea and lower GI bleeding. CT scan showed evidence of colitis and liver lesions. Colonoscopy showed areas of friable mucosa. Biopsies were obtained.
**Penicillium marneffei**

- Dimorphic fungus
- Endemic in Southeast Asia and Far Eastern Asia
- Now one of the most common opportunistic infections in Asian patients with AIDS
- Most commonly involves lungs and liver, followed by GI tract
P. marneffei

- Inflammatory response is granulomatous, suppurrative, or mixed
- Yeast forms are septate ("pill capsule") and similar to histoplasmosis, but they do not bud
  - Occasional elongated "sausage" forms with prominent septum
- Require months of antifungal therapy, and dissemination can be rapidly fatal
# Characteristics of Yeast in Tissue Sections

<table>
<thead>
<tr>
<th>Fungus</th>
<th>Exposure</th>
<th>Histology</th>
<th>Stains</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Histoplasma capsulatum</em></td>
<td>Ohio/MS river valleys</td>
<td>Uniformly small oval yeast with buds at pointed pole; “Halo” in tissue</td>
<td>GMS, PAS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Usually in macrophages</td>
<td></td>
</tr>
<tr>
<td><em>P. marnefeii</em></td>
<td>Asia</td>
<td>Small nonbudding septated yeast</td>
<td>GMS, PAS</td>
</tr>
<tr>
<td><em>Cryptococcus neoformans</em></td>
<td>Worldwide</td>
<td>Variably sized yeast with narrow based buds</td>
<td>GMS, PAS, Melanin Mucicarmine</td>
</tr>
<tr>
<td><em>Blastomyces dermatitidis</em></td>
<td>Ohio and MS river valleys</td>
<td>Large yeast with broad based buds</td>
<td>GMS, PAS, Gram negative</td>
</tr>
<tr>
<td></td>
<td>Great Lakes NW Ontario</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Candida torulopsis</em></td>
<td>Worldwide</td>
<td>Small budding yeast</td>
<td>GMS, PAS</td>
</tr>
</tbody>
</table>
Case Example

• A 46 year old HIV-positive man presented with fever and weight loss. CT scan showed mesenteric lymphadenopathy. A mesenteric lymph node biopsy was performed.
Atypical (non-Tubercular) Mycobacteria

• Ubiquitous soil, milk, food, and water inhabitants
• Four major groups that cause infections all over the body
• MAI is most commonly encountered
  – AIDS, other immunocompromising conditions
MAI

- Inflammatory reaction very variable:
  - Site of infection
  - Immune status of host
  - Patterns:
    - Foamy histiocyte infiltrate
    - Epithelioid granulomas
    - Spindle cell nodule
    - Fibrin ring granuloma
Mycobacteria-Dx Approach

• History is critical
• Fresh tissue?
  – Culture
  – DNA probes
• No fresh tissue?
  – AFB stains
  – Molecular
    • Not useful if AFB stain is negative
MAI-Differential Diagnosis

- *M. tuberculosis*
  - Culture, PCR
  - Different inflammatory reaction (usually)
- Other atypical mycobacteria
- Nocardia
- Other neoplasms (spindle cell nodule)
  - AFB stain
  - CD68
  - Mycobacteria will stain with desmin, actin, keratin
Species Matters

- Diagnosis not final just because it’s not MTb
- All atypicals are not MAI
- Therapy varies by species
- If you see organisms but PCR is negative, doesn’t mean you hallucinated, just that block is exhausted
Pseudomembranous Colitides
Case Example

• An 85 year old woman who resided in a nursing home, with multiple medical problems, was put on antibiotics for a skin infection. Within two weeks, she developed severe diarrhea that was blood-tinged. She was admitted to the hospital, and a colonoscopy was performed.
C. difficile

- Most common nosocomial GI pathogen
- Almost always associated with antibiotic use
  - New abx exposure
  - Multiple abx
- Recurrence is common despite successful therapy, and incidence of recurrent disease is increasing
C. difficile

• Other risk factors:
  – Old age (80 or older)
  – PPI/H2 blocker use
  – Hospitalization within past 2 months
  – Chemotherapy
  – Steroids
C. difficile-Diagnosis caveats

• May superinfect IBD
• May co-exist with other pathogens
• May not show typical pseudomembranes
  – Acute infection-type colitis pattern
  – Fulminant colitis pattern
• Other organisms cause pseudomembranes
Pseudomembranous Colitis

- **C. difficile**
  - "Volcano" lesion, Exploding crypts, Pseudo-signet ring cells
  - Cultures not useful
  - C. diff toxin assay usually positive
  - Abx associated

- **Shigellosis**
  - Mimics C. diff
  - Cultures +
  - C. diff toxin assay –
  - Food, travel associated

- **EHEC**
  - Mimics ischemia
  - Cultures +
  - C. diff toxin assay –
  - Food associated

- **Ischemia**
  - Crypt withering, lamina propria hyalinization
  - Cultures –
  - C. diff toxin assay –
  - Atherosclerosis, low-flow, estrogens, coagulopathy, illicit drugs, vasculitis
C. difficile: Lab Diagnosis

- Toxins A and B
  - BI/NAP1 strain-hypervirulent strain with increased production of both toxins
- Stool toxin assays: high specificity (65-100%), limited sensitivity (31-99%); negative assay does not exclude C. difficile
C. difficile Lab Diagnosis

- FDA-Approved PCR Assays
  - Sensitivity 77-100%; Specificity 93-99%
  - Higher sensitivity than EIA means repeat testing in 7 days not needed
  - Positive result does not mean bacteria is viable and cannot assess severity of disease
  - Correlation with endoscopy, morphology, toxin assays remains controversial
References