Bacterial and Viral Infections Mimicking IBD

Murat Toruner
Ankara University Medical School
Ankara - TURKEY
Outline

• Summary of clinical manifestations of Ulcerative colitis

• Summary of clinical manifestations of Crohn’s disease

• Differential diagnosis of inflammatory bowel diseases

• Specific bacterial and viral infections mimicking inflammatory bowel diseases
Clinical Manifestations of Ulcerative Colitis

- Bloody diarrhea,
- Passage of mucus,
- Crampy pain,
- Tenesmus,
- Fever,
- Weight loss,
- Poor nutritional status,
- Anemia due to blood loss
Clinical Manifestations of Crohn’s Disease

- Abdominal pain,
- Diarrhea
- Fever,
- Weight loss,
- Perianal pain and drainage (perianal disease)
- Anemia
Disorders may Simulate IBD

• Infectious Agents
  - Salmonella
  - Shigella
  - Escherichia coli
  - Campylobacter jejuni
  - Yersinia
  - Tuberculosis
  - Ameoba
  - CMV
  - C. Difficile

• Inflammatory diseases
  - Diverticulitis
  - Collegenous colitis

• Vascular agents
  - Ischemic
  - Radiation

• Neoplasms
  - Lymphoma
  - Adenocarcinoma
  - Carcinoid

• Motility disorders
  - Irritable bowel syndrome
  - Solitary rectal ulcer

• Iatrogenic factors
  - NSAIDs
  - Endoscopic cleaning solution reaction
Distinction of Infections from IBD is Important

• Clinical presentations may be similar or overlapping,

• Treatment options are totally different,
  - Immunomodulators and corticosteroids are the main choices for IBD treatment,
  - Biological therapies are being used more common in recent years
Intestinal Tuberculosis

• Tuberculosis is a rare (but increasing) infection in western countries,

• TB is caused by an acid-fast bacilli - Mycobacterium Tuberculosis

• Intestinal involvement is seen in ~ 1% of patients,

• Diagnosis of isolated intestinal tuberculosis is always challenging
• **Pathogenesis:**
  - Swallowing infected sputum,
  - Hematogenous spread from active pulmonary or miliary Tb,
  - Ingested of contaminated food or milk,
  - Contiguous spread from adjacent organs

• **Macroscopic appearance of intestinal lesions:**
  - Ulcerative (multiple ulcers) - 60%
  - Hypertrophic (fibrosis, pseudotumors) - 10%
  - Ulcerohypertrophic (characterized by an inflammatory mass centering around the ileocecal valve with thickened and ulcerated intestinal walls) - 30%
• **Symptoms:**
  - Abdominal pain,
  - Diarrhea,
  - Night sweat,
  - Weight loss,
  - Right quadrant mass,
  - Fatigue

• **Localization:**
  - Ileo-ceecal,
  - Jejuno-ileum
  - Colon and rectum
Diagnosis

- PPD

- Detection of acid-fast bacilli in tissue or stool,

- Culture for M. Tuberculosis (reliable but results in 4-6 weeks)

- PCR of the biopsy specimens
IBD vs. Intestinal TB

• Serological Tests?
  - Not helpful!

<table>
<thead>
<tr>
<th></th>
<th>HC (n=21)</th>
<th>UC (n=25)</th>
<th>CD (n=59)</th>
<th>IT (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCA Ig A</td>
<td>4.7%</td>
<td>28%</td>
<td>33.9%</td>
<td>43.3%</td>
</tr>
<tr>
<td>ASCA Ig G</td>
<td>4.7%</td>
<td>24%</td>
<td>50.8%</td>
<td>46.6%</td>
</tr>
</tbody>
</table>

# IBD vs. Intestinal TB

- Colonoscopy + Biopsy ---- Diagnostic procedure of choice

<table>
<thead>
<tr>
<th></th>
<th>TB (n=33)</th>
<th>CD (n=31)</th>
<th>PPV (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Favoring TB</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large Granulomas</td>
<td>17</td>
<td>0</td>
<td>100</td>
<td>80.5, 100</td>
</tr>
<tr>
<td>&gt;4 sites of granulomatous inflammation</td>
<td>15</td>
<td>0</td>
<td>100</td>
<td>78.2, 100</td>
</tr>
<tr>
<td>Caseation</td>
<td>9</td>
<td>0</td>
<td>100</td>
<td>66.4, 100</td>
</tr>
<tr>
<td>Band of epithelioid histiocytes in ulcer base</td>
<td>20</td>
<td>0</td>
<td>100</td>
<td>83.2, 100</td>
</tr>
<tr>
<td>Granulomatous inflammation in caecum</td>
<td>22</td>
<td>4</td>
<td>84.6</td>
<td>65.1, 95.6</td>
</tr>
<tr>
<td><strong>Favoring CD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-tuberculcous granulomas</td>
<td>2</td>
<td>19</td>
<td>90.48</td>
<td>69.6, 98.8</td>
</tr>
<tr>
<td>Mucosal changes distant to sites with granulomas</td>
<td>0</td>
<td>17</td>
<td>100</td>
<td>80.5, 100</td>
</tr>
<tr>
<td>Focal crypt-related inflammation</td>
<td>3</td>
<td>10</td>
<td>76.92</td>
<td>46.2, 94.9</td>
</tr>
<tr>
<td>Granulomas in sigmoid or rectum</td>
<td>5</td>
<td>11</td>
<td>68.75</td>
<td>41.3, 88.9</td>
</tr>
</tbody>
</table>

Pulimood AB et al., JGH (2005) 20: 688-96
IBD vs. Intestinal TB

Clinical and Histopathological findings help to differentiate Intestinal TB from CD

- **Intestinal TB**
  - Chest X-ray
  - Confluent granulomas
  - => 10 granulomas per biopsy site
  - Caseous necrosis
  - Ulcers lined by conglomerate epithelioid histiocytes
  - Disproportionate submucosal inflammation

- **CD**
  - Perianal fistulae
  - Extra-intestinal manifestations

IBD vs. Intestinal TB

Colonoscopic findings may help to differentiate Intestinal TB from CD

- Findings more frequent in CD
  - Anorectal lesions,
  - Longitudinal ulcers,
  - Aphthous ulcers,
  - Cobblestone appearance

- Findings more frequent in TB
  - Involvement of fewer than four segments,
  - A patulous ileocecal valve,
  - Transverse ulcers,
  - Scars or pseudopolyps

Lee YJ et al., Endoscopy (2006) 38: 592-7
Treatment

- Treatment of intestinal tuberculosis is primarily medical and consists of a four-drug regimen;
  - Isoniazid,
  - Rifampicin,
  - Pyrazinamide,
  - Either streptomycin or ethambutol
CMV Colitis

- Cytomegalovirus – present in a latent state in most people (50% - 80% of whole population),

- A member of Herpesviridae family,

- Acquired either at birth or transmitted through sexual or parental exposure,

- Antigenic stimuli or immune suppression leads to CMV activation
  - If it happens in bowel wall, then called as Gastrointestinal CMV disease
Gastrointestinal CMV disease can occur in:

- Patients with acquired immune deficiency syndrome (AIDS),
- Patients after transplantation,
- Patients receiving cancer chemotherapy,
- Infants,
- Elderly people,
- Patients with inflammatory bowel disease
Symptoms:

• Fever
• Abdominal pain,
• Diarrhea, bloody diarrhea
• Hematochezia
Diagnosis

- **Colonoscopy**
  - Patchy erythema, deep ulcers, multiple mucosal erosions etc.
  - Mostly in right colon

- **Histology**
  - Cytoplasmic inclusions
    - H&E sensitivity 10% - 87%, IHC sensitivity 93%

- **Serology**
  - CMV Ig M, CMV Ig G

- **CMV antigen test**
  - Detects late structural protein pp65 -- semi-quantitative and results are subjective

- **CMV DNA test**
  - Cut-off levels ??? 400 - 10000 copies/mL ??

- **CMV culture**
  - Conventional culture - low sensitivity
  - Rapid viral culture - low sensitivity
CMV colitis does not occur only in immunosuppressed patients!

- Meta-analysis 1980-2003
- 44 patients
- Immunocompetence
  - No transplantation
  - No congenital immunodeficiency
  - No acquired immunodeficiency
  - No immunosuppressive treatment
- Female patients survive better
- Younger patients (<55) survive better
- Patients treated with antivirals survived better than patients who had colectomy
CMV & IBD

- IBD patients – usually immunosuppressed (corticosteroids etc.)

- Flare of IBD or Steroid refractory IBD – Think CMV infection!

- CMV infection is seen frequently in IBD patients,
  - 22% in Ulcerative colitis (resection materials)
    - Maconi G et al., Dig Liver Dis (2005) 37: 418-23
  - 13% in Ulcerative colitis (resection materials)
    - Cooper HS et al., Gastroenterology (1977) 72: 1253-6
  - 18% in steroid refractory UC + CD
Does CMV infection occur only with corticosteroid use?

- Prospective study,
- Consecutive 42 IBD patients,
- CMV detection - Histology and/or antigenemia
- CMV infection prevalence - 21% (9/42)
- Subgroup of CS refractory IBD - 33% (4/12)

How do we treat CMV colitis?

- **Ganciclovir** (nucleoside analog) is the choice of treatment, 5 mg/kg every 12 hr 3-5 days, then,
- **Oral valganciclovir** should be initiated to complete 2-3 week treatment,
- **Myelosuppression** - 40% patients

- **Foscarnet** - Resistance or intolerance to Ganciclovir, 90 mg/kg IV, every 12 h, 2-3 week
- **Side effects** (Nephrotoxicity, CNS effects etc.) - 33% patients
How to manage CMV infection in IBD patients?

Treat? Not Treat?
No consensus!

5 steroid responsive IBD patients, only 1 treated with antiviral; 100% remission

10 IBD patients, all received antiviral, 70% remission, 10% death, 20% no response
Clostridium Difficile

- Gram-positive, spor forming rod

- Present naturally in the environment (more commonly on contaminated hospital surfaces),

- Antibiotics disturb the natural flora and decrease the resistance to C. Difficile colonization,

- Once colonized, several factors (mainly host’s immune system) determine whether a person become symptomatic,
Clostridium Difficile

• Produce three toxins,
  - Toxin A
  - Toxin B (1000 x cytotoxic)
  - Binary toxin (role in human disease unknown)

• Toxin A and B,
  - Induce fluid secretion,
  - Induce apoptosis of intestinal epithelial cells
  - Induce a marked inflammation
Risk factors for C. Difficile associated Diarrhea

- Increasing age,
- Severe underlying disease,
- Non-surgical gastrointestinal procedures,
- Presence of a nasogastric tube,
- Receiving anti-ulcer medication,
- Stay on intensive care unit,
- Multiple antibiotic use,
- Long hospital stay,
Symptoms

- Diarrhea (mostly watery, rarely bloody)
- Fever
- Crampy abdominal pain
**Diagnosis**

- **Cytotoxicity assay (gold standard)**
  - requires 48 hours
  - 100-1000 x sensitive than EIA in detecting toxin B

- **Enzyme Immunoassay**
  - Detect
    - Toxin A and B
    - Toxin A alone
  - Sensitivity 80% per stool, 3 examination required

- **Endoscopy**
  - Pseudomembranes (typical)
  - Erythema, edema, friability, and nonspecific colitis with small ulcerations (non-specific)
Treatment

- Indications for antibiotic treatment:
  - Evidence of colitis (leukocytosis, endoscopic findings etc.) or severe diarrhea,
  - Persistent diarrhea despite cessation of offending antibiotic treatment,
  - A need to continue antibiotic therapy to treat the underlying infection

- Antibiotic choices:
  - Metranidazole (drug of choice), 500 mg tid, 10-14 days
  - Vancomycin (alternative first line drug), 125 mg qid, 10-14 days
  - Fucidic acid, 500 mg tid, 10 days
  - Nitazoxanide 500 mg bid, 10 days
C. Difficile and IBD

• C. Difficile, one of the infections should be tested in refractory IBD,

• Incidence of C. Difficile infection in IBD is increasing;
  - Between 1998-2004, CDAD rates in UC tripled (18.4 to 57.6/1000) and in CD doubled (9.5 to 22.3/1000)
    Rodemann JF et al., Clin Gastroenterol Hepatol (2007) 5: 339-44
  - Rate of C.Difficile infection increased from 1.8% in 2004 to 4.6% in 2005.
    Issa M et al., Clin Gastroenterol Hepatol (2007) 5: 345-51
C. Difficile and IBD

- Colonic involvement and maintenance immunomodulator use are independent risk factors for C. Difficile infection.

- The majority contracted infection as an outpatient (76%),
  
  Issa M et al., Clin Gastroenterol Hepatol (2007) 5: 345-51

- Treatment:
  - Metranidazole
  - Vancomycin
  - Fusidic acid
  - Nitazoxanide
**Campylobacter Jejuni Infection**

- Motile, non-spore forming, comma shaped, gram negative rods,
- The vast reservoir in animals is probably the ultimate source for most Campylobacter infections in humans,
- Direct contact with infected animals and fecal-oral person to person transmission have been reported,
- Incubation period varies from 1-7 days,
- The sites of intestinal inflammation includes jejunum, ileum and colon,
Campylobacter Jejuni Infection

- **Gross examination reveals:**
  - Diffuse, bloody, edematous and exudative enteritis

- **Histological features include:**
  - Inflammatory infiltrate of neutrophils, mononuclear cells and eosinophils in the lamina propria,
  - Ulceration of mucosal epithelium,
  - Crypt abscesses
Symptoms and Clinical Manifestations

- Fever,
- Abdominal pain (crampy),
- Diarrhea (Watery [initial], bloody [progressed]),
- Toxic megacolon (in very severe disease),
- Enlarged mesenteric lymph nodes,
- Reactive arthritis (HLA-B27 positive)
- Meningitis, Endocarditis (very rare)
- Guillain-Barre Syndrome (1:2000 cases)
• Prevalence of Campylobacter infection in relapsing IBD - 1.5% to 4.5%


**Diagnosis**

• Direct examination of feces (in 2 hrs after passage),
  - Characteristic “darting” motility of microorganism,
  - Red blood cells and neutrophils

• Stool and blood culture
  - Microaerobic conditions
Treatment

• Erythromycin (Drug of choice) 500 mg bid, 5-7 days
• Azithromycin - 30 mg/kg single dose

• Macrolide resistance ~ 5% and stable

• Floroquinolones;
  - Effective in treatment but,
  - Increasing resistance is a problem (~19%)
Yersinia Enterocolitica

- Pleomorphic gram-negative bacilli,

- Can be acquired by oral ingestion or direct inoculation (i.e. blood transfusion etc.)

- Produce several proteins those facilitate adherence of microorganism to the gut mucosa, binding epithelial cells and invasion of gut wall,

- Once the organism has invaded, Yersinia enterocolitica localizes in lymphoid tissue within the gut wall and in regional mesenteric lymph nodes
Symptoms and Clinical Manifestations

- Frequency of clinical signs and symptoms differ in outbreaks compared to sporadic (non-outbreak associated) cases

- Diarrhea,
- Bloody diarrhea,
- Vomiting,
- Fever,
- Abdominal pain,
- Sore throat
Variety of gastrointestinal and extra-intestinal complications of Yersiniosis have been described.

<table>
<thead>
<tr>
<th>Gastrointestinal</th>
<th>Extra Gastrointestinal</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Supurative appendicitis</td>
<td>• Erythema Nodosum</td>
</tr>
<tr>
<td>• Diffuse ulcerative ileitis or colitis</td>
<td>• Reactive arthritis (HLA B27 +)</td>
</tr>
<tr>
<td>• Intestinal perforation</td>
<td>• Septicemia</td>
</tr>
<tr>
<td>• Peritonitis</td>
<td>• Endocarditis</td>
</tr>
<tr>
<td>• Toxic megacolon</td>
<td>• Meningitis</td>
</tr>
<tr>
<td>• Necrotic small bowel</td>
<td>• Osteomyelitis</td>
</tr>
<tr>
<td>• cholangitis</td>
<td>• Septic arthritis</td>
</tr>
<tr>
<td></td>
<td>• Empyema</td>
</tr>
<tr>
<td></td>
<td>• Suppurative lymphadenitis</td>
</tr>
<tr>
<td></td>
<td>• Skin manifestations (carbuncle, granuloma, vesiculobullous lesions, pustules, wound infection).</td>
</tr>
</tbody>
</table>
Diagnosis

• Culture
  - Stool (remains positive for weeks after acute infection)
  - Throat, lymph nodes, blood, joint fluid, etc.

• Serology
  - Agglutination assays
  - ELISA
  - Immunoblotting
Treatment

- Treatment of acute, non-complicated yersiniosis is not beneficial,

- Most cases of Yersinia enterocolitis do not require treatment,

- Treatment of an individual case should be judged clinically necessary because of clinical severity or underlying condition of the patient (e.g., immunocompromised patients),

- Drug of choices are fluoroquinolones such as ciprofloxacin (500 mg twice daily) or trimethoprim-sulfamethoxazole for the pediatric patient (TMP 8 mg/kg per day and SMX 40 mg/kg per day in two divided doses).
Escherichia Coli

• Gram negative rod, is a portion of normal enteric flora,

• There are 3 different categories of pathogenic E.Coli causing colitis,
  - Enterohemorrhagic E. Coli
  - Enteroinvasive E.Coli
  - Enteroaggregative E.Coli
Enterohemorrhagic E. Coli

- Have >50 serogroups, the major strain is 015:H7
- Cause non-invasive inflammation, product 2 shiga-like toxins (SLT1 and SLT2),
- Symptoms occur 3-4 days after infection;
  - Watery diarrhea
  - Bloody diarrhea
  - Fever
  - Abdominal pain
- Diagnosis is made by stool culture
- Lesions are present in terminal ileum and colon, confused with ischemic injury
- Treatment is supportive, antibiotics are not effective.
• **Enteroinvasive E. Coli**
  - Causes infection similar to Shigellosis,
  - There is direct invasion of the distal ileal and colonic mucosa
  - Occurs primarily in tropics, rarely in western countries

• **Enteroaggregative E. Coli**
  - Cause inflammation by both adhesion to epithelial cells and by toxin elaboration,
  - Occurs mainly in children in tropics
  - Ciprofloxacin 500 mg PO, bid
Salmonella Infection

- Caused by gram-negative rods,
- Most commonly reportable cause of diarrhea in the U.S
- Infections occur through contaminated food or water,
- Organism invades the epithelium of the ileum and colon,
- Symptoms:
  - Nausea
  - Vomiting
  - Fever
  - Watery or bloody diarrhea
- Illness is self-limited and resolves usually in 2 to 5 days
Shigella Infection

• Caused by gram negative bacilli

• The second most reportable cause of infectious diarrhea in the U.S.

• Organism invades enterocytes and induce apoptosis,

• Organism produces toxins, both shiga and shiga like toxins, which inhibit protein synthesis

• Symptoms;
  - Watery diarrhea,
  - Fever,
  - Abdominal pain
  - Rectal tenesmus
  - Mucus and blood passage per rectum

• Usually self-limited and there is no need to treat unless there is a complicated infection (Ciprofloxacin 500 mg PO, bid)
Summary

• Ulcerative colitis and Crohn’s disease account only a small proportion of the number of patients with inflammatory colitis,

• Majority of inflammatory colitis are due to infectious causes,

• Infectious causes can mimic IBD or trigger the activation of IBD

• Differential diagnosis between IBD and infectious colitis is important to treat patients adequately.