Inflammatory Bowel Disease (IBD)

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IBD

- Chronic, idiopathic inflammatory disease of gastrointestinal tract:
  - Crohn’s disease (CD) and Ulcerative colitis (UC).
  - The incidence of IBD varies within different geographic areas.
  - In Asia and South America, IBD is rare.
  - The highest mortality in IBD patients is during the first years of disease and in long duration disease (>10 years) due to the risk of colon cancer.
  - The peak age of onset 15 and 30 years. A second peak: 60 and 80.

UC: Etiology and pathogenesis:

- Multigenic disorder; no single gene variant is sufficient to produce disease while environmental triggers are necessary for the disease expression in susceptible individuals
- Enhanced level of lamina propria T cells activation
- Smokers commonly - CD while non smokers- UC
- Appendectomy protects against UC.

Pathology

- Mucosal disease that usually involves the rectum and extends proximally to involve all or part of the colon.
- Approximately 40 to 50%: rectum and rectosigmoid, 30 to 40%: extending beyond the sigmoid but not whole colon, 20%: total colitis.
- Proximal spread: continuity without areas of uninvolved mucosa.
- Mild inflammation: mucosa is erythematous and has a fine granular surface (looks like sandpaper).
- Severe disease: hemorrhagic, edematous, and ulcerated.

Pathology

- In long-standing disease: inflammatory polyps (pseudopolyps) may be present as a result of epithelial regeneration.
- Remission: mucosa may appear normal in but in patients with many years of disease it appears atrophic and featureless and the entire colon becomes narrowed and foreshortened.

Histologic findings:

- Mucosa and superficial submucosa involved (deeper layers unaffected except in fulminating disease).
- Two major histologic features are:
  1. the crypt architecture of the colon is distorted; crypts may be bifid and reduced in number;
  2. some patients have basal plasma cells and multiple basal lymphoid aggregates.
- Mucosal vascular congestion with edema and focal hemorrhage, and an inflammatory cells are infiltrate
Clinical presentation

- Diarrhea, rectal bleeding, tenesmus, passage of mucus, and crampy abdominal pain.
- The severity of symptoms correlates with the extent of disease.
- Symptoms usually have been present for weeks to months.
- Occasionally, diarrhea and bleeding are so intermittent and mild: patient does not seek medical attention.

Clinical presentation

- Extends beyond the rectum, blood is usually mixed with stool, or grossly bloody diarrhea may be noted.
- Severe disease: a liquid stool containing blood, pus, and fecal matter.
- Diarrhea is often nocturnal and/or postprandial.
- Other symptoms in moderate to severe disease include anorexia, nausea, vomiting, fever, and weight loss.

Clinical presentation

Physical signs

- Proctitis: a tender anal canal and blood on rectal exam.
- More extensive disease: tenderness to palpation directly over the colon.
- Toxic colitis: severe pain and bleeding.
- Megacolon: hepatic tympany.
- Toxic colitis & Megacolon may have signs of peritonitis if a perforation has occurred.

Table 1. UC assessment of disease activity

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
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<tbody>
<tr>
<td>Stool/ day</td>
<td>&lt;4 per day</td>
<td>4-6 per day</td>
</tr>
<tr>
<td>Blood in stool</td>
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<td>Moderate</td>
</tr>
<tr>
<td>Fever</td>
<td>None</td>
<td>37.5°C mean</td>
</tr>
<tr>
<td>Pulse (bpmm)</td>
<td>&lt;90</td>
<td>90-100</td>
</tr>
<tr>
<td>Anemia</td>
<td>Mild</td>
<td>&gt;75%</td>
</tr>
<tr>
<td>Hemeocrit(%)</td>
<td>Normal</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>Normal</td>
<td>3-3.5</td>
</tr>
<tr>
<td>FSR</td>
<td>&lt;20</td>
<td>20-30</td>
</tr>
<tr>
<td>Weight loss (%)</td>
<td>None</td>
<td>1-10</td>
</tr>
</tbody>
</table>

Laboratory, Endoscopic, and Radiographic Features

- Active disease: a rise in acute phase reactants (C-reactive protein), platelet count, erythrocyte sedimentation rate (ESR)
- Anemia:
- Albumin: In severely ill patients will fall rather quickly.
- Leukocytosis may be present.

Laboratory, Radiographic and Endoscopic Features

- Single-contrast barium enema
  1. The earliest radiologic change: a fine mucosal granularity.
  2. Severe: the mucosa becomes thickened and superficial ulcers
  3. Deep ulcerations can appear as “collar-button” (the ulceration has penetrated the mucosa).
  5. Colon becomes shortened and narrowed.
  6. Polyps: pseudopolyps, adenomatous polyps, or carcinoma.
  7. Sigmoidoscopy: disease activity is often performed before treatment.
A narrowed sigmoid colon without haustration in a patient with extensive colitis for about 30 years.

The descending colon (D), narrowed and without haustration. In the oral part of the transverse colon (T) there are some haustration.

The appearance of a normal colon at endoscopy

An inflamed colon that is typical for the appearance of UC at endoscopy.

Severe UC: The mucosa is grossly denuded, with active bleeding noted.

Severe ulcerative colitis in rectum (to the left) and in sigmoid colon (to the right).
inflammatory polyp

Severe IBD in the sigmoid colon, UC to the left and CD to the right

ulcers in the intestine that are typical for Crohn’s disease.

Diagnosis:

Essential of diagnosis:
- Bloody diarrhea
- Lower abdominal cramps and fecal urgency
- Anemia, low serum albumin
- Negative stool examination for bacteria Clostridium difficile toxin / ova / parasites
- Sigmoidoscopy is the key to diagnosis.

differential diagnosis

UC and CD have similar features to many other diseases. Once a diagnosis of IBD is made, distinguishing between UC and CD is impossible in 10 to 20% of cases. These are termed indeterminate colitis.

Differential diagnosis

Infectious disease: bacterial, fungal, viral, or protozoal in origin.
1. Bacterial disease: Diagnosis of is made by sending stool specimens for bacterial culture and C. difficile toxin analysis.
2. Gastrointestinal TB: Distal ileal and cecum involved, present with diarrhea, constipation, abdominal pain, weight loss, fever, night sweating, malabsorption, and small bowel obstruction and a tender abdominal mass. The diagnosis: colonoscopy with biopsy and culture.
Noninfectious disease

**Ischemic colitis:** Colonic inflammation due to ischemia may resolve quickly or may persist and result in transmural scarring and stricture formation.
- Elderly pts. following abdominal aortic aneurysm repair or when a patient has a hypercoagulable state or a severe cardiac or peripheral vascular disorder.
- Sudden onset of left lower quadrant pain, urgency to defecate, and the passage of bright red blood per rectum.
- Endoscopic: a sharp transition to an area of inflammation in the descending colon and splenic flexure.

Complications:
- **Massive hemorrhage:** occurs with severe disease (1% of patients) and treatment for the disease usually stops the bleeding. If patients require 6 to 8 units of blood within 24 to 48 h, colectomy is indicated.
- **Toxic megacolon:** transverse colon with a diameter of more than 5.0 cm to 6.0 cm, with loss of haustration; occurs in patients with severe disease.
  1. About 5% of attacks and can be triggered by electrolyte abnormalities and narcotics.
  2. Approximately 50% resolve with medical therapy alone, but urgent colectomy is required for those not improved.

**Complications:**

- **The risk of neoplasia:** increases with duration and extent of disease. For patients with pancolitis, the risk of cancer rises 0.5 to 1% per year after 8 to 10 years of disease.
- **Obstructions:** caused by benign stricture formation occur in 10% of patients, with one-third of the strictures occurring in the rectum. These should be surveyed endoscopically for carcinoma.

Inflammatory Bowel Disease Crohn's disease (CD)

**Pathogenesis**

- Genetic and environmental factors.
- The cellular events involved in the pathogenesis involve activation of macrophages, lymphocytes and polymorphonuclear cells.
- Release of inflammatory mediators leads.

**Pathology**

- Mucosal lesion typically begins as aphthous ulcer.
- Progressively ulcer deepens, enlarges, and appear as linear strictures;
- The changes are patchy,
- Macosa between them is normal (cobblestone).
- Deep ulcers may initiate abscesses / fistulae. Fistulae betn loops of bowels or betn affected bowel and bladder, uterus or vagina and may appear in the perineum.
- The mesenteric lymph nodes enlarged.
- Histologically, transmural inflammation is the characteristic findings.
- Nonnecrotizing (non-caseating) granulomas are other characteristic findings.

Clinical findings:
- Intermittent exacerbations separated by periods of complete/relative remission.
- Few pts has ongoing, persistent symptoms.
- Presentation depends on the site of disease
clinical presentation includes inflammatory, stricture, and perforating.

Clinical findings:
- Ileal disease:
  1. Abdominal pain
  2. subacute intestinal obstruction, an inflammatory mass, intra-abdominal abscess or acute obstruction.
  3. With watery diarrhoea and no blood or mucus.
  4. lose weight (coz eating provokes pain/ malabsorption).
- Crohn’s colitis:
  1. bloody diarrhoea, passage of mucus may present;
  2. lethargy, malaise, anorexia, weight loss.

P.E. & Lab findings:
Recall sparing and the presence of perianal disease are features suggest CD.
- P.E.: • weight loss, anaemia, glossitis and angular stomatitis, abdominal tenderness; • abdominal mass (thickened bowel or abscess); • Perianal skin tags, fissures or fistulae are found in at least 50% of patients.
  - Mild leukocytosis; anemia; raised ESR; CRP +ve; hypoalbuminemia. Stool: WBC +ve; but no pathogen in e/s.

Imaging:
- Contrast radiography of GI:
  1. provides invaluable information in the dx and t/t.
  2. demonstrate the lesions/fistula/or perforation/abscess etc.
  3. Characteristic findings are: skip lesions; cobblestoning, stricture.
  4. CT is not helpful in diagnosis but need for complications.

Colonoscopy:
is the procedure of choice for the evaluating the presence/extent of disease.
Classical finding includes
  - aphthae (small shallow ulcer with a red halo);
  - round or linear ulcer; in between ulcer there is normal mucosa;
  - and rectal sparing.
  - Biopsies: non-necrotizing granuloma.
Oral ulcerations

Small aphtous ulcers like these in the rectal mucosa are diagnostic for CD

Deep long sharply marginated ulcers are typical findings in active CD

Complications: Perforating disease:
- may lead to abscess (is rare)/fistula formation.
- 20% have abscess (intraabdominal type- common; located within mesentiec or between loops; extrabdominal-retroperitoneum and abdominal wall).
- 40% have fistula (between bowel — cause diarrhoea and malabsorption due to blind loop syndrome / bladder—recurrent urinary infections and pneumaturia / vagina — feculent vaginal discharge); occurs with CD only.
- Fistulation from the bowel may also cause perianal or ischiorectal abscesses, fissures and fistulae.

Complications

Strictures:
- recurrent stricture formation is the hallmark of CD.
- Obstructive symptoms are due to stricture/or acute inflammation and edema/mass effect of abscess.
- partial obstruction—conservative management.

Perirectal disease: anorectal fisture; abscess.
Enteroenteric fistula: Note that barium is just starting to enter the cecum in the right lower quadrant, but that barium has also started to enter the sigmoid colon, indicating small bowel to the sigmoid colon fistula.

Complications

Nutritional deficiencies:
- malnutrition due to reduced intake / vomiting / diarrhea / fat malabsorption / bile salt depletion with secondary B12 deficiency etc.

Cancer:
- extensive active colitis of more than 8 years duration is at increased risk of colon cancer.
- Surveillance colonoscopy is to be started after 8-10 years of diagnosis.

Stricture in the terminal ileum noted during colonoscopy.

Diagnosis and DD

Essentials of diagnosis of CD
- Insidious onset
- Intermittent bouts of lower-grade fever, diarrhea, and right lower quadrant pain
- Right lower quadrant mass and tenderness
- Perianal disease with abscess, fistulas
- Radiographic evidence of ulceration, structuring, or fistula of the small intestine or colon.

Treatment

Sulfasalazine/5-ASA Agents:
- The mainstay of therapy for mild to moderate UC and CD
- Sulfasalazine broke down in the colon by bacterial azo reductases into sulfa and 5-ASA moieties.
- Sulfasalazine is effective in inducing and maintaining remission in mild to moderate UC and CD ileocolitis and colitis, but its high rate of side effects limits its use.
- Sulfasalazine: 500mg BD and increased gradually over 1-2 weeks to 2-3g BD.
- Sulfasalazine can also impair folate absorption and patients should be supplemented with folic acid.
5-ASA, mesalamine

- Newer sulfite-free aminosalicylate preparations deliver increased amounts of the pharmacologically active ingredient to the site of active bowel disease while limiting systemic toxicity.
- Inhibition of NF-κB activity.
- Dose of 1.2-2.4g/d for active disease.
- Topical mesalamine enemas are effective in mild-to-moderate distal UC and CD (esp disease limited to the distal 10 cm rectum).
- Mesalamine suppositories, at doses of 500 mg twice a day are effective in treating proctitis.

Glucocorticoids:

- Limited distal disease who fail to respond to topical or oral 5-ASA: hydrocortisone enemas (100mg) once/twice daily.
- Moderate to severe UC/CD: oral or parenteral glucocorticoids.
- Prednisone 40 to 60mg/d for active UC that is nonresponsive to 5-ASA therapy (after 2-4 week treatment) and after induction of remission within 1-2 weeks steroids should be tapered slowly by 5mg/week over 6-8 weeks.
- Steroids have no role in maintenance.
- Parenteral glucocorticoids: IV hydrocortisone 300mg/d or methylprednisolone 40 to 60mg/d.

Antibiotics: Metron/ Cipro

These two antibiotics should be used as second-line drugs in active CD after 5-ASA agents and as first-line drugs in perianal and fistuluous CD.
- Metronidazole
  - Effective in active inflammatory, fistulous, and perianal CD and may prevent recurrence after ileal resection.
  - 15 to 20mg/kg per day in three divided doses; usually continued for several months.
- Ciprofloxacin (500 mg bid)
  - Is also beneficial for inflammatory, perianal, and fistuluous CD.

Azathioprine and 6-Mercaptopurine

- Commonly employed in the RX of glucocorticoid-dependent IBD.
- Are inhibitor of purine ribonucleotide synthesis and cell proliferation.
- Efficacy is seen at 3 to 4 weeks.
- Azathioprine (2.0 to 2.5 mg/kg per day) or 6-MP (1.0-1.5 mg/kg per day) have been employed successfully weaned from glucocorticoids in up to 2/3 of UC and CD patients.
- Well tolerated, side effects include: pancreatitis occurs (within first few weeks) in 3 to 4% of patients; leukopenia.

Methotrexate; MTX

- Inhibits dihydrofolate reductase, resulting in impaired DNA synthesis.
- IM or IH MTX (25 mg per week) is effective in inducing remission and reducing glucocorticoid dosage and 15 mg per week is effective in maintaining remission in active CD.
- MTX should only be used when either 6-MP or azathioprine are ineffective or poorly tolerated.

Cyclosporine

- Alters the immune response by acting as a potent inhibitor of T cell-mediated responses.
- CSA is most effective given at 4 mg/kg per day IV in severe UC that is refractory to IV glucocorticoids.
- CSA can be an alternative to colectomy.
- Oral CSA alone is only effective at a higher dose (7.5 mg/kg per day) in active disease but is not effective in maintaining remission without 6-MP/azathioprine.
- Serum levels monitored and kept in the range of 200-400 ng/mL.
- CSA has the potential for significant toxicity, and monitor renal function.
Surgical Therapy for UC

- Indication: Intractable disease; fulminant disease; Toxic megacolon; Colonic perforation; Massive colonic hemorrhage; Extracolonic disease; Colonic obstruction; Colon cancer prophylaxis; Colon dysplasia or cancer.
- Morbidity is about 20% in elective, 30% for urgent, and 40% for emergency proctocolectomy.
- The risks are primarily hemorrhage, contamination and sepsis, and neural injury.

SURGERY for CD

- The indications for surgery are: fistulae, abscesses and perianal disease, and small or large bowel obstruction.
- Up to 80% of patients eventually need surgical intervention but, still have disease recurrence.
- Strictureplasty: for those who have multiple or recurrent strictures. Stricture is not resected but instead incised in its longitudinal axis and sutured transversely.