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IBD

★ Objectives:

- **Describe & Distinguish the Inflammatory bowel disease (IBD) is comprised of two major disorders: Ulcerative colitis (UC), Crohn's disease (CD).**
- **Know the disorders have both distinct and overlapping pathologic and clinical characteristics.**
- **Know the Genetic factors: NOD2/CARD15**
- **Know the ENVIRONMENTAL FACTORS: Smoking, Appendectomy: protect UC, Diet**

★ Resources Used in This lecture:

Step up to medicine - Master of board -Doctor's slides - Doctor notes

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Inflammatory Bowel Disease

Definition

Idiopathic disorder Composed of Two presentation Crohn's Disease and Ulcerative colitis , both distinct and overlapping pathologic and clinical characteristics.

Epidemiology:

- More common in the west and developed countries such as Canada
- More common in Caucasians than other racial groups.
- Mean age (peak) is 15 to 35 years, and there is second peak at age of 50.

Etiology:

Both diseases has no clear cause, but there multiple factors which hypothesized to Play Role:

1- Environmental factors

- **Smoking** : increase a chance crohn's disease and seen to have a protected role in Ulcerative colitis.
- **Appendectomy** is seen to have a protected role in Ulcerative colitis
- **Persistent infection**
- **Defective mucosal integrity**: because it leads increase susceptibility of antigen to go from gut into blood which → autoimmune response
- **Dysbiosis** (change in microbiota of the gut) . I
- **Dysregulated immune response**

2-Diet : Western diet and Frozen food increase a chance of IBD especially in child before 10 years

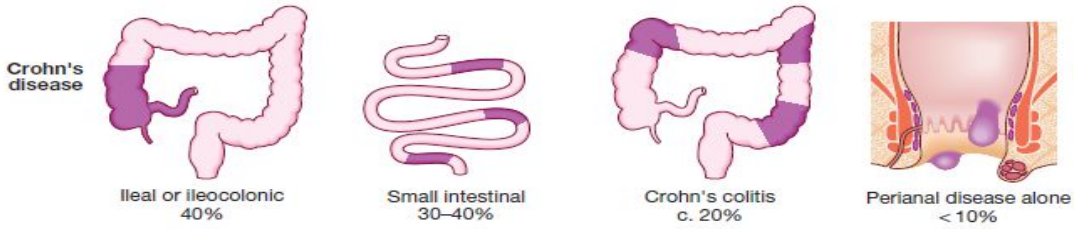
3-Genetic factors: NOD2/CARD15 increase a chance of IBD and it's mainly found in western Caucasian, Ashkenazi Jews).

Crohn's Disease

Location

Can affect any part of the GI tract (from mouth to anus). Most commonly affect the small bowel, specifically the **terminal ileum**

- 40% to 50% of patient have the disease in the **terminal ileum and cecum (ileocolic)**
- 30% of patient have the disease confined to the **small intestine**
- 20% to 25% patient have the disease confined to the **colon**
- Rarely (less than 5%) affect **(mouth, stomach, esophagus)**.



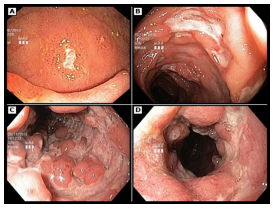
Clinical features:

- ❑ Diarrhea (usually without blood)
- ❑ Abdominal pain (usually RLQ pain), nausea and vomiting
- ❑ Malabsorption and weight loss
- ❑ Fever, Fatigue and malaise
- ❑ Extraintestinal manifestation : Uveitis ., Arthritis , aphthous oral ulcers ,pyoderma gangrenosum

Pathology :

- ❑ Skip lesions : patchy discontinuities pattern of inflammation
- ❑ Noncaseating granulomas
- ❑ Fistulas and abscess
- ❑ Strictures of the lumen
- ❑ Cobble stones appearance of the mucosa (due to discontinuities pattern of inflammation)
- ❑ Mesenteric "Fat creeping"
- ❑ Presence of lymphocyte

Diagnosis



- ❑ **Endoscopy with biopsy (Colonoscopy Or sigmoidoscopy)**
- ❑ **Imaging: MR enterography**
- ❑ **Serological Test :presence of** Anti-Saccharomyces cerevisiae antibodies (ASCA) **,used when the diagnosis is unclear .**
- ❑ **Stool marker (fecal calprotectin) : differentiate between IBS and IBD.**

Note

- **Endoscopy is most accurate test**
- **Wireless capsule endoscopy : used especially in pediatric patients**
- **Upper GI with small bowel follow-through and CT enterography now not used anymore**
- **Whenever a patient present to you, <u>ROLE OUT INFECTION!</u>**

Complications

1- Fistulae

Between bowel and other viscus:

- With other loop of the intestine (enteroenteral)
- With bladder (enterovesical)
- Vagina (enterovgainal)
- With skin (enterocutaneous)

2- Small bowel obstruction : Most common indication for surgery.

- Initially, happen because edema and spasm "intermittent"
- Later, happen because of scarring and thickening of the wall "chronic continuous"

3- Anorectal diseases[1] (in 30%)

Includes fissures, abscesses, perianal fistulas (almost exclusively to Crohn's)

4- Malignancy " less common than in UC"

5-Malabsorption (of vit B_{12} and bile acids >> in terminal ileum)

6- Cholelithiasis[2] (due to decreased bile acid absorption → stone)

7-Nephrolithiasis (due to increased oxalate absorption → stone)

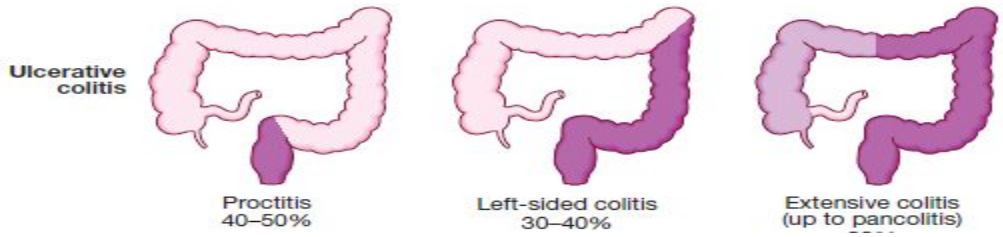
8- Aphthous ulcers in lips, gingiva and buccal mucosa

9-Toxic megacolon (more in UC)

Ulcerative Colitis

Location

It involved the RECTUM in most all of the cases, with variety of involving the rest of the colon.(Start in **rectum** then extend proximally)



- Ulcerative proctitis (Rectum alone)10%
- Left sided colitis (from rectum to the splenic flexure) (40%)
- Pancolitis (whole colon) (30%)
- Extensive colitis (from rectum to the to hepatic flexure" (30%)
- UC does not usually involve the small bowel, but in small percentage it may reach the terminal ileum (called **backwash ileitis**)

[1]

[2] Remember that Bile Salt reabsorption is located in the ileum and in case of crohn's disease the ilium more likely to be affected. So, the absorption of Bile Salt will be less → loss of equilibrium in the Bile content → Increase the chance of getting Gallstones.

Clinical features:

- ❏ Hematochezia (bloody diarrhea)
- ❏ Mucus in the stool
- ❏ Crampy abdominal pain
- ❏ Tenesmus
- ❏ Bowel movement are frequent but small quantities (because it involves the colon, opposite to that, if the small bowel is the site, will be large quantities)
- ❏ Fever, anorexia, nausea, vomiting and weight loss
- ❏ Extraintestinal manifestation (will be discussed)

Pathology

1-continuous inflammation of the rectum and/or colon (No skip or patchy lesions)
2-The inflammation in confined to the mucosa or submucosa (no transmural)
3-Crypt abscesses (Polymorphonuclear cells accumulate in the crypts of the colon)
4-Chronic changes : branching of crypts, atrophy of glands, and loss of mucin in goblet cells

Complications

1-Hemorrhage > anemia
2-Perforation
3-Strictures, benign and malignant (usually malignant)
4- Colon cancer[3]
5-Toxic megacolon (main cause of death in UC patient)
6-Cholangiocarcinoma (50% of bile duct cancer associated with UC)
7-Primary sclerosing cholangitis (the course of PSC is not parallel with UC, i.e. not affected by colectomy or the attacks of UC)
8-Electrolyte disturbances and dehydration (due to diarrhea)

Diagnosis of IBD

Lab test :

- ❏ Fecal leukocyte : Positive → Stool culture (to role our infection)
- ❏ **Stool marker (fecal calprotectin) : differentiate between IBS and IBD.**

Specific test :

- ❏ **Endoscopy with biopsy (Colonoscopy Or sigmoidoscopy)**
- ❏ **Imaging: MR enterography**
- ❏ **Serological Test : used when the diagnosis is unclear .**
- Anti-Saccharomyces cerevisiae antibodies (**ASCA) → crohn's**
- Antineutrophil cytoplasmic antibodies **(pANCA) → UC**

Note :

- **Endoscopy is most accurate test**
- **Wireless capsule endoscopy : used especially in pediatric patients**
- **Upper GI with small bowel follow-through and CT enterography now not used anymore**
- **Whenever a patient present to you, ROLE OUT INFECTION!**

[3] *After 8 years from the diagnosis of Ulcerative colitis, Yearly surveillance for colon cancer is made.*

Management of IBD

1. **Medical Therapy**

❑ **5-ASA (5-aminosalicylic acid compounds or aminosalicylates):**

❑ **Ex:** Sulfasalazine, Mesalamine compounds Oral (Asacol, pentasa. Rectal(Canasa, Rowasa)

- **MOA:** Induce and maintain remission by anti-inflammatory effect (inhibit prostaglandins and leukotrienes)
- **Side effect (of sulfasalazine):** Crystalluria ,BM depression, Megaloblastic anemia,Folic acid deficiency.

❑ **Metronidazole: if no response to 5-ASA**

❑ **Corticosteroids: Systemic**: Prednisolone. Local (rectal): Budesonide: used For acute exacerbation and if there is no response to metronidazole (used to Induce remission)

❑ **Immunomodulators (**Azathioprine , methotrexate)

- **MOA :** Azathioprine "Inhibit purine synthesis", methotrexate "folic acid antagonist"
- **Used :** In conjunction with steroids if the patient does not respond to the previous drugs

❑ **Anti-TNF therapy (i**nfliximab, Adalimumab,Certolizumab)

- **MOA**: Inhibit TNF-α and it has higher response in CD than UC
- **Used** : in fistula or severe disorder unresponsiveness to

2. **Nutrition therapy (for crohn's)**

❑ **Bile acid sequestrant (**cholestyramine, colestipol)

3. **SURGICAL THERAPY :** Used For complications ,Failure of medical therapy and Severe disability

❑ **crohn's →** segmental resection with anastomosis

❑ **UC → (** total resection **)**

Remember:

- **Surgery in crohn's not curative due high recurrence rate , while in UC is curative.**

Extraintestinal manifestations of IBD

1-Arthritis (most common extraintestinal manifestation of IBD)
- Migratory monoarticular arthritis "parallel to bowel disease activity- with exacerbation of colitis"
- Ankylosing spondylitis[4] (UC patient are 30 times higher to get it) "not parallel to disease activity"
- Sacroiliitis "not parallel to disease activity"

2-Eye lesions
- **Episcleritis** "parallel to disease activity"
- **Anterior uveitis** "not parallel to disease activity"

3-Skin lesions
- **Erythema nodosum**[5] (more in Crohn's) "parallel to disease activity"
- **Pyoderma gangrenosum**[6] (more in UC) "parallel to disease activity in 50%"

4-Primary Sclerosing cholangitis in UC (jaundice presentation)[7]
5-Venous and arterial thromboembolism can lead to DVT,PE and CVA
6- Bone loss and osteoporosis
7-Gallstones (more in Crohn's)[12]
8-Renal stones (more in Crohn's)[1]

Summary:

22.70 Comparison of ulcerative colitis and Crohn's disease

	Ulcerative colitis	Crohn's disease
Age group	Any	Any
Gender	M = F	Slight female preponderance
Incidence	Stable	Increasing
Ethnic group	Any	Any; more common in Ashkenazi Jews
Genetic factors	*HLA-DR*103*; colonic epithelial barrier function (*HNF4a, LAMB1, CDH1*)	Defective innate immunity and autophagy (*NOD2, ATG16L1, IRGM*)
Risk factors	More common in non-/ex-smokers Appendicectomy protects	More common in smokers
Anatomical distribution	Colon only; begins at anorectal margin with variable proximal extension	Any part of gastrointestinal tract; perianal disease common; patchy distribution, skip lesions
Extra-intestinal manifestations	Common	Common
Presentation	Bloody diarrhoea	Variable; pain, diarrhoea, weight loss all common
Histology	Inflammation limited to mucosa; crypt distortion, cryptitis, crypt abscesses, loss of goblet cells	Submucosal or transmural inflammation common; deep fissuring ulcers, fistulae; patchy changes; granulomas
Management	5-ASA; corticosteroids; azathioprine; biological therapy (anti-TNF); colectomy is curative	Corticosteroids; azathioprine; methotrexate; biological therapy (anti-TNF); nutritional therapy; surgery for complications is not curative; 5-ASA not effective

(5-ASA = 5-aminosalicylic acid; TNF = tumour necrosis factor)

[4] Ankylosing spondylitis (AS) is a chronic progressive inflammatory arthropathy predominantly affecting the spine and sacroiliac joints. Patients present with severe pain and spinal stiffness
[5] Erythema nodosum- nodules affect extensor part of limbs, painful, response to steroid, no scar formation
[6] Pyoderma gangrenosum- ugly ulceration, usually painless, leave a scar
[7] With elevated Alkaline phosphatase and/or GGT

MCQs:

Q1: A 24-year-old woman presents to her primary care provider because of bloody diarrhea for several months and uveitis. Complete blood cell count shows mild anemia but a normal WBC count. The erythrocyte sedimentation rate and the C-reactive protein level are not elevated.
Which of the following is the most likely diagnosis?
A. Bacterial enterocolitis
B. Bowel ischemia
C. Colon carcinoma
D. Mallory-Weiss tear
E. Ulcerative colitis

Q2: Crohn's disease may produce all of the following EXCEPT:
A. vesicovaginal fistula
B. Rectovesical fistula
C. Perianal fistula
D. Jejuno-colic fistula
E. Enterocutaneous fistula

Q3: A 30-year-old male with ulcerative colitis develops jaundice, pruritus, and right upper quadrant pain. Liver biopsy shows an inflammatory obliterative process affecting intrahepatic and extrahepatic bile ducts.
What's the most likely diagnosis?
A. Sclerosing cholangitis
B. Hepatitis D
C. Wilson's disease
D. Gallstones

Q4:All of the following are complication of Ulcerative colitis, EXCEPT:
A. Arthritis
B. Pyoderma gangrenosum
C. Uveitis
D. Aphthous ulcer
E. Toxic Megacolon

Q5:A 25-year-old white man presents to the emergency department with diarrhea, weight loss of 4.5 kg (10.0 lb) over the preceding 2 months, and RLQ pain. His temperature is 38.2°C (100.7°F), heart rate is 82/min, and blood pressure is 110/70 mmHg. Abdominal examination reveals mild tenderness with no rebound tenderness, and a mass is

palpated in the RLQ. His stool tests positive for occult blood. Subsequent colonoscopy reveals erythematous, friable mucosa with ulcerations in a longitudinal distribution. The ulcerations are segmental and interspersed with intervening normal mucosa. Colonic biopsies show a dense inflammatory infiltrate with neutrophils and mononuclear cells.

The patient should be informed of which of the following?

A. Antibiotics have been shown to benefit patients with his condition
B. Appendectomy should be scheduled
C. Curative proctocolectomy with ileoanal anastomosis is indicated at this time
D. Toxic megacolon is a frequent complication of his disease
E. Trial gluten-free diet is indicated

Answers: 1.E , 2.A , 3.A , 4.D , 5.A

Long case 1

History

A 34-year-old woman presents to her general practitioner (GP) complaining of a rash. Over the past 2 weeks she has developed multiple tender red swellings on her shins and forearms. The older swellings are darker in colour and seem to be healing from the centre. She feels generally unwell and tired and also has pains in her wrists and ankles. She has not had a recent sore throat. Over the past 2 years she has had recurrent aphthous ulcers in her mouth. She has had no genital ulceration but she has been troubled by intermittent abdominal pain and diarrhoea. She works as a waitress and is unmarried. She smokes about 15 cigarettes per day and drinks alcohol only occasionally. She has had no other previous medical illnesses and there is no relevant family history that she can recall.

Examination

She is thin but looks well. There are no aphthous ulcers to see at the time of the examination. Her joints are not inflamed and the range of movement is not restricted or painful. Examining the skin there are multiple tender lesions on the shins and forearms. The lesions are raised and vary from 1 to 3 cm in diameter. The fresher lesions are red and the older ones look like bruises. Physical examination is otherwise normal.

Investigations		Normal
Haemoglobin	13.5 g/dL	11.7–15.7 g/dL
White cell count	15.4×10^9/L	$3.5–11.0 \times 10^9$/L
Platelets	198×10^9/L	$150–440 \times 10^9$/L
ESR	98 mm/h	<10 mm/h
Sodium	138 mmol/L	135–145 mmol/L
Potassium	4.3 mmol/L	3.5–5.0 mmol/L
Urea	5.4 mmol/L	2.5–6.7 mmol/L
Creatinine	86µmol/L	70–120 µmol/L
Glucose	5.8 mmol/L	4.0–6.0 mmol/L

Chest X-ray: normal **Urinalysis: normal**

What is the diagnosis ?
What is the major causes of this condition ?

Answer:

This patient has erythema nodosum, in this case secondary to previously undiagnosed Crohn's disease. Erythema nodosum is due to inflammation of the small blood vessels in the deep dermis. Characteristically it affects the shins, but it may also affect the thighs and forearms. The number and size of the lesions is variable. Lesions tend to heal from the centre and spread peripherally. The rash is often preceded by systemic symptoms – fever, malaise and arthralgia. It usually resolves over 3–4 weeks, but persistence or recurrence suggests an underlying disease.

Diseases linked to erythema nodosum :

- Streptococcal infection
- Tuberculosis
- Leprosy
- Glandular fever
- Histoplasmosis
- Coccidioidomycosis
- Lymphoma/leukaemia
- Sarcoidosis
- Pregnancy/oral contraceptive
- Reaction to sulphonamides
- Ulcerative colitis
- Crohn's disease

The history of mouth ulcers, abdominal pain and diarrhoea strongly suggests that this woman has Crohn's disease. She should therefore be referred to a gastroenterologist for investigations which should include a small-bowel enema and colonoscopy with biopsies.Treatment of her underlying disease with steroids should cause the erythema nodosum to resolve. With no serious underlying condition, erythema nodosum usually settles with non-steroidal anti-inflammatory drugs.

Points to consider:

• Patients presenting with erythema nodosum should be investigated for an underlying disease.
• Erythema nodosum is most often seen on the shins but can affect the extensor surface of the forearms or thighs.

Long case 2

History

A 35-year-old woman has a year-long history of intermittent diarrhoea which has never been bad enough for her to seek medical help in the past. However, she has become much worse over 1 week with episodes of bloody diarrhoea 10 times a day. She has had some crampy lower abdominal pain which lasts for 1–2 h and is partially relieved by defecation. Over the last 2–3 days she has become weak with the persistent diarrhoea and her abdomen has become more painful and bloated over the last 24 h. She has no

relevant previous medical history. Up to 1 year ago, her bowels were regular. There is no disturbance of micturition or menstruation. In her family history, she thinks one of her maternal aunts may have had bowel problems. She has two children aged 3 and 8 years. They are both well. She travelled to Spain on holiday 6 months ago but has not travelled elsewhere. She smokes 10 cigarettes a day and drinks rarely. She took 2 days of amoxicillin after the diarrhoea began with no improvement or worsening of her bowels.

Examination

Her blood pressure is 108/66 mmHg. Her pulse rate is 110/min, respiratory rate 18/min. Her abdomen is rather distended and tender generally, particularly in the left iliac fossa. Faint bowel sounds are audible. The abdominal X-ray shows a dilated colon with no faeces.

Investigation		Normal
Haemoglobin	11.1 g/dL	11.7–15.7 g/dL
Mean corpuscular volume (MCV)	79 fL	80–99 fL
White cell count	$8.8x10^9$/L	$3.5–11.0x10^9$/L
Platelets	$280x10^9$/L	$150–440x10^9$/L
Sodium	139 mmol/L	135–145 mmol/L
Potassium	3.3 mmol/L	3.5–5.0 mmol/L
Urea	7.6mmol/L	2.5–6.7 mmol/L
Creatinine	89 µmol/L	70–120 µmol/L

What is your interpretation of these results?
What is the likely diagnosis and what should be the management?

Answer:

Bloody diarrhoea 10 times a day suggests a serious active colitis. In the absence of any recent foreign travel it is most likely that this is an acute episode of ulcerative colitis on top of chronic involvement. The dilated colon suggests a diagnosis of toxic megacolon which can rupture with potentially fatal consequences. Investigations such as sigmoidoscopy and colonoscopy may be dangerous in this acute situation, and should be deferred until there has been reasonable improvement. The blood results show a microcytic anaemia suggesting chronic blood loss, low potassium from diarrhoea (explaining in part her weakness) and raised urea, but a normal creatinine, from loss of water and electrolytes.

If the history was just the acute symptoms, then infective causes of diarrhoea would be higher in the differential diagnosis. Nevertheless, stool should be examined for ova, parasites and culture. Inflammatory bowel disorders have a familial incidence but the patient's aunt has an unknown condition and the relationship is not close enough to be helpful in diagnosis. Smoking is associated with Crohn's disease but ulcerative colitis is more common in non-smokers.

She should be treated immediately with corticosteroids and intravenous fluid replacement, including potassium. If the colon is increasing in size or is initially larger than 5.5 cm then a

laparotomy should be considered to remove the colon to prevent perforation. If not, the steroids should be continued until the symptoms resolve, and diagnostic procedures such as colonoscopy and biopsy can be carried out safely. Sulphasalazine or mesalazine are used in the chronic maintenance treatment of ulcerative colitis after resolution of the acute attack.

In this case, the colon steadily enlarged despite fluid replacement and other appropriate treatment. She required surgery with a total colectomy and ileo-rectal anastomosis. The histology confirmed ulcerative colitis. The ileorectal anastomosis will be reviewed regularly;there is an increased risk of rectal carcinoma.

Points to consider

• Bloody diarrhoea implies serious colonic pathology.
• It is important to monitor colonic dilatation carefully in colitis, and vital to operate before rupture.
• Both Crohn's disease and ulcerative colitis can cause a similar picture of active colitis.