INFLAMMATORY BOWEL DISEASE (IBD)

- Crohn's disease (CD) & Ulcerative colitis (UC) are chronic relapsing inflammatory disorders of unknown (idiopathic) origin, collectively known as idiopathic inflammatory bowel disease (IBD), which share many common features.

- IBD result from an abnormal local immune response against the normal flora of the gut & probably against some self antigens, in genetically susceptible individuals.

- CD may affect any portion of the GIT from esophagus to anus, but most often involves the ileum (terminal ileitis).

- 50% of cases exhibit noncaseating granulomatous inflammation

- UC is a nongranulomatous disease limited to the colon.
CD & UC differ in many respects, including the disease natural history, pathological aspects, treatment & responses to treatment.

Before considering these diseases separately, the pathogenesis of both CD & UC will be considered.

Etiology & Pathogenesis of both CD & UC

The normal intestine is in a steady state of "physiologic" inflammation, representing a dynamic balance between

عنا هجوم وعنا دفاع

(1) Factors that activate the host immune system, such as luminal microbes, dietary antigens, & endogenous inflammatory stimuli; &

(2) Host defenses that down-regulate inflammation & maintain the integrity of the mucosa.

The search for the causes of loss of this balance in CD & UC has revealed many parallels,
but the origins of both diseases remain unexplained (thus their designation as *idiopathic*).

*idiopathic* = *primary* or *essential*

The Genetic Predisposition, Immunologic Factors, & Microbial Factors will be discuss.

**Genetic Predisposition**

► There is little doubt that genetic factors are important in the occurrence of IBD.

# First-degree relatives are 3 to 20 times more likely to develop the IBD.

# 15% of persons with IBD have affected first-degree relatives.

In keeping with an underlying immunologic dysfunction, both CD & UC have been linked to specific major histocompatibility complex class II alleles.

| UC | 30% of CD cases in North American white males. |
One of every 8 patients with IBD has a first-degree relative with the disease and this suggests the importance of genetic factors in the diagnosis of these diseases.

**Immunologic Factors**

# It is not known whether the immune responses in IBD are directed against self-antigens of the intestinal epithelium? or to bacterial antigens?

It means immune response is not known.

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→ In both CD & UC, the primary damaging agents appear to be CD4+ cells.

The inflammatory cytokine TNF may play an important pathogenic role in CD; this is suggested by the effectiveness of treatment with TNF antagonists in CD.
The sites affected by IBD—the distal ileum & the colon—are awash {covered by tides} in bacteria.

While there is no evidence that these diseases are caused by microbes, it is quite likely that microbes provide the antigenic trigger to a fundamentally dysregulated immune system.

Mمكن انه البكتيريا بالإضافة انه الشخص اصلا عند عنده triggering the disease ب يكون الها دور ب immune system.
This concept is strengthened by the observations that in murine models, IBD develops in the presence of normal gut flora but not in germ-free mice.

The Final Common Pathway for the Pathogenesis of IBD is Inflammation, which is ultimately, the result of activation of inflammatory cells (neutrophils initially & mononuclear cells later) in the course, causing mucosal destruction & the intermittent bloody diarrhea that is characteristic of IBD.

Most current therapeutic interventions act entirely or partly through nonspecific down-regulation of the immune system.
Among diagnostic tests, the most useful is the detection of perinuclear antineutrophil cytoplasmic Abs, which are present in 75% of persons with UC only 11% of individuals with CD.

**Crohn’s Disease (CD)**

**Epidemiology**

- Worldwide in distribution, CD is much more prevalent in the US, GB, & Scandinavia than in Central Europe, & is rare in Asia & Africa.

- The incidence & prevalence of CD has been steadily raising in the US & Western Europe, with annual incidence in the US of 4 per 100,000 populations (12000 new cases/Year)
It occurs at any age, from young childhood to advanced age, but peak incidence is between the 2nd & 3rd decades of life.

Females are affected slightly more often than males.

Whites appear to develop the disease 2 to 5 times more often than do nonwhites.

In the US, CD occurs 3 to 5 times more often among Jews than among non-Jews.

CD may affect any level of the GIT, from mouth to anus, but most commonly located at the terminal ileum. At first, the disease was thought to be limited to the ileum, & that is why it was referred to as "terminal ileitis" or "regional enteritis".

BUT, CD must be viewed as a systemic inflammatory disease with predominant GIT involvement.
Active cases of the disease are often accompanied by extra-intestinal complications of immune origin, such as uveitis, sacroiliitis, migratory polyarthritis, erythema nodosum, bile duct inflammatory disorders, & obstructive uropathy.

► GROSSLY

∙ Site: In CD there is gross involvement of the small intestine alone, of both small intestine & colon, or colon alone. Sites are distinctly uncommon. May involve the mouth, esophagus, stomach, & duodenum.
*Fully developed CD characterized by:*

→ Classically, sharply limited, & demarcated diseased bowel segments from adjacent uninvolved bowel.

الحد القاطع ما بين normal intestine و lesion عن خط واضح جدا

→ Transmural inflammation involving all the bowel wall, with

→ Mucosal damage → Fissuring → Fistula formation

تششققات Fissuring ما بين ال loop and abdominal wall او Fistula formation vagina and bladder احيانا

→ Noncaseating granulomas in 50% of cases,

• The intestinal wall is rubbery & thick, the result of edema, inflammation, fibrosis, & hypertrophy of the muscularis propria.

As a result, the lumen is almost always narrowed; in the small intestine this is seen radiographically as → "string"
"sign," a thin stream of barium passing through the diseased segment

 Segmental narrowing affected by Crohn disease

 - In diseased segments, the serosa becomes granular & dull gray & often the mesenteric fat wraps around the bowel surface → ("creeping fat")

 - When several bowel segments are involved, the intervening bowel is essentially normal ("skip" lesions).

 In the intestinal mucosa, early disease shows focal mucosal...

 - ulcers, resembling aphthous ulcers, edema, & loss of the normal mucosal texture.

 oral cavity يلي حكيناها ب ulcers هاي في البداية بتكون تشبه
Later, ulcers coalesce into long, serpentine linear ulcers, which tend to be oriented along the axis of the bowel (F15-30 & 4.39).

Later, the axis of the bowel tends to be oriented along the axis of the bowel (F15-30 & 4.39).

zig zag Serpentine

Because the intervening mucosa tends to be relatively spared, it acquires a coarsely textured, cobblestone appearance.

Fissures develop between the folds of the mucosa, often penetrating deeply through the bowel wall all the way to the serosa. This may lead to...

Damage of mucosa >>> ulceration >>> Cobblestone >>> Fissures
Adhesions with adjacent loops of bowel. Further extension of fissures leads to...

- Fistula or sinus tract formation to adherent viscera, surface

Fistula or sinus tract may be form between 2 loops of intestine to the skin or ........ sometimes to vagina or urinary bladder

{Summary: Cobblestone & Ulcers → Fissures → Adhesions → Sinus → Fistula → Abscess}.
H, mucosa show characteristic features:

1. **Inflammation**, with neutrophilic infiltration into the epithelial layer (*cryptitis*) & accumulation within crypts to form crypt abscesses;

2. Ulceration, &

3. Chronic mucosal damage, distortion & atrophy.

(4) Granulomas may be present any-where in the GIT, even in individuals with CD limited to one bowel segment.

However, the absence of granulomas does not exclude the diagnosis of CD.

50% of CD cases contain noncaseating Granulomas in the involved area.

La Zam Tazhek Anhe Hei affecting mucosa, submucosa, muscularis, serosa

UC Hada Usan Nimez Between and Between

Which only affecting mucosa and submucosa
(5) In diseased segments, the muscularis mucosae & muscularis propria are usually markedly thickened, & fibrosis affects all bowel layers (Transmural inflammation).

ال فبيروس نتيجة رح يؤدي ل wall (Transmural inflammation).

intestinal obstruction وبعدين widening

(6) Lymphoid aggregates scattered through the full intestinal wall & in the extramural fat are characteristic.

lymphoid aggregates الموجود قريب على intestine extramural fat

Particularly important in persons with long-standing chronic CD are dysplastic changes appearing in the mucosal epithelial cells.

Long-standing

These may be focal or widespread, tend to increase with time, & predispose to a X 5-6 folds increased risk of carcinoma, particularly of the colon.

dysplasia
Clinically, the presentation of CD disease is highly variable & unpredictable.

لا يعرف شو المستقبل تبعه ومتغير

(1) The dominant manifestations are recurrent episodes of diarrhea & crampy abdominal pain.

(2) In most patients, after an initial attack, the manifestations remit either spontaneously or with therapy, but characteristically they are followed by relapses, & intervals between successive attacks grow shorter.

(3) Superimposed on this course are the potential development of malabsorption & some of the extra-intestinal manifestations mentioned earlier.

The debilitating consequences of CD include
The severe effects:

1) Fistula formation to other loops of bowel, urinary bladder, vagina, or perianal skin;

2) Abdominal abscesses or peritonitis;

3) Intestinal stricture or obstruction.

***Rare devastating events are:

1) Massive intestinal bleeding,

2) Toxic dilation of the colon, or PERITONITIS

3) Ca of the colon or small intestine.

Although the increased risk for CA is significant, it is substantially less than that associated with UC.

No matter the increased risk of cancer in chronic ulcerative disease, it is still less than that associated with UC.

Ulcerative Colitis (UC)
• UC is an inflammatory-ulcerative disease affecting the colon only not involving the small intestine, which is limited to the mucosa & submucosa, except in the most severe cases.

• Like CD, UC is a systemic disorder associated in some persons with migratory polyarthritis, sacroiliitis, ankylosing spondylitis, uveitis, erythema nodosum, & hepatic involvement (pericholangitis a & primary sclerosing cholangitis).

• There are several important differences between UC & CD the most important are:

  • In UC:

  • Superficial colonic mucosal ulcers, rarely extend below the submucosa & there is surprisingly little fibrosis, which means ...
Serosal surface is completely normal.

- No Mural thickening; there are no muscle fibrosis.
- No granulomas, &
- No skip lesions, there appears to be a continuous lesions.
- High risk of carcinoma development in the colon.
F15-32: Comparison of the distribution patterns of Crohn disease & ulcerative colitis, & the different conformations of the ulcers & wall thickenings.

**Formation of crypt abscesses/ involvement by fissure and fistula / localized abscess formation**

 Skipping lesions CD be a lesion transmural, and it leads to formation of crypt abscesses/ involvement by fissure and fistula / localized abscess formation.

Re: UC, it can appear in the superficial mucosa and cause a pseudopolyp.
Epidemiology

♠ UC is slightly more common (Double) than CD in the US & Western countries, with an incidence of around 7 per 100,000 populations, but it is infrequent in Asia & Africa.

CD ضعف الحالات تبعت

♠ As with CD, the incidence of UC has risen in recent decades.

التنين بزدوا حاليا

In the US it is more common among whites than among nonwhites & exhibits no particular sex predilection (F=M).

♠ UC may arise at any age, with a peak incidence between ages 20 & 25 years.

وللاسف حاليا حالات متزايدة بالاطفال

♠ UC has a familial association; 20% of persons with the UC have affected relatives.

20 بالمئة من الاشخاص المصابين عندهم اقارب بهاد المرض
Individuals with UC & ankylosing spondylitis have an increased frequency of the HLA-B27 allele, but this association is related to the spondylitis & not to UC.

► GROSSLY,

😊 UC usually involves the rectum & sigmoid & much less frequently involves the entire colon (pancolitis from ilioseecal valve to anal canal).

Da'ima ta'dakhr ha b'da'iti b rectum, sigmoid wa ba'din yin'tash ali sha'lik pancolitis la yowj bi'nha manakat na'masa ba'halat na'dara kl cowlun you have to creat pouch from small intestine total colectomy wa'ha'i taxmai.

😊 Colonic involvement is continuous from the distal colon, so that skip lesions are not encountered.

😊 Active UC denotes ongoing inflammatory destruction of the mucosa, with gross hyperemia, edema, granularity with friability & easy bleeding, while you touch it by endoscope.

chronic wa' active yeli hi acute

mucosa bkon tdmir shama'al la acute
In severe UC there is extensive & broad-based ulceration of the mucosa in the distal, or the whole colon aligned along its long axis.

Isolated islands of regenerating mucosa bulge upward to create pseudopolyps (mucosal tags).

In rare cases, the muscularis propria is so compromised as to permit perforation & pericolonic abscess formation.

Exposure of the muscularis propria & neural plexus to fecal material also may lead to complete shutdown of neuromuscular function.
When this occurs, the colon progressively swells & becomes gangrenous (toxic megacolon).

وحدة من الخواطر الهائلة ب باهذة عادة تؤدي الى ucgangrenous hugely dilated (toxic megacolon)

►►► death

♣ The pathologic features of UC are

· those of mucosal inflammation, ulceration, & chronic mucosal damage.

· A diffuse, predominantly mononuclear inflammatory infiltrate in the lamina propria is almost universally present,

· Neutrophilic infiltration of the epithelial layer may produce collections of neutrophils in crypt lumina (crypt abscesses), which are not specific for UC & may be observed in CD or any active infective inflammatory colitis (inf by bacterial infection).

· Unlike CD, there are no granulomas

مو موجود ب CD ب5 بالمئات من حالات مع انه موجود ب uc مو موجود ب

· Further destruction of the mucosa leads to outright ulceration, extending into the submucosa.
· With remission of active disease, granulation tissue fills in the ulcer craters, followed by regeneration of the mucosal epithelium.

Submucosal fibrosis & mucosal architectural disarray (shorter +branching ) & progressive mucosal atrophy leads to a flattened & attenuated mucosal surface, which remain as residua of healed disease ( inactive stage )

Ulceration in mucosa and submucosa >>>regeneration in remission >>> fibrosis in submucosa + mucosal architectural disarray (shorter +branching ) & progressive mucosal atrophy ......

😊 The most serious complication of UC is the development of ! colon carcinoma.

Two factors govern the risk: duration of the disease & its anatomic extent.
<table>
<thead>
<tr>
<th>It is believed that limited to the left colon</th>
<th>With pancolitis</th>
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<td>With 10 years of UC at 20 years 20 years By 30 years</td>
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<td>the risk is minimal the risk is on the order of 2% the risk of carcinoma is 10% 15% to 25%</td>
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Long standing UC is premalignant, and you can advice the patient to remove colon to avoid this highly dangerous complication.

Overall, the annual incidence of colon cancer in persons with UC of more than 10 years' duration is 1%.
Clinical Features of UC

∙ UC is a chronic relapsing disease marked by attacks of bloody mucoid diarrhea that may persist for days, weeks, or months & then subside, only to recur later.

∙ Presentation is usually insidious (gradual), with cramps, tenesmus, & colicky lower abdominal pain that is relieved by defecation.

∙ Grossly bloody stools are more common with UC than with CD, & the blood loss may be considerable.

∙ Extra-intestinal manifestations, particularly migratory polyarthritis, are more common with UC than with CD.

☹ Uncommon but life-threatening complications include

∙ severe diarrhea & electrolyte derangements,

∙ massive hemorrhage,
· severe colonic dilation (toxic megacolon) with potential rupture, perforation & peritonitis.

▼ Diagnosis can usually be made by endoscopic examination & biopsy.

· Specific infectious causes must always be ruled out

يعني إذا كان عند المريض لازم حتى نستبعد سبب infection

يعني إذا كان عند المريض لازم لازم لازم لازم bloody diarrhea and ulceration حتى نستبعد سبب bloody stool examination and culture
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