Diseases of the GI tract
2018
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Lecture 7: inflammatory bowel disease
Introduction

- In lectures 7-9 we will discuss diseases of the large intestine.

- These are common and important diseases, and I will concentrate mainly on two important diseases: inflammatory bowel disease which I will discuss in this lecture and neoplastic diseases which will be discussed in lecture 8. Lecture 9 will discuss the rest of the large intestinal diseases.
Inflammatory bowel disease (IBD)

- this is a chronic inflammatory disease affecting the intestine.
- It results from inappropriate mucosal immune activation.
- there are two diseases in this entity: Crohn’s disease and ulcerative colitis.
Epidemiology

- More common in females.
- First presentation in adolescence or early adulthood.
- Incidence worldwide is increasing; probably due to improved hygiene (hygiene hypothesis): reduced enteric infections during childhood cause inadequate development of regulatory processes that limit mucosal immune response.
Patients with IBD have a chronic inflammation in their intestine.

This inflammation is thought to occur due to an abnormal immune response to the microflora in their GI tract. Changes in microflora and defects in the epithelium enhance this response in genetically susceptible individuals.

So: let’s try to understand the components of this puzzle…. See next slide!
Pathogenesis

• the exact pathogenesis of IBD is not fully understood but several factors play a role in the development of IBD

A. Genetic factors

B. Mucosal immune responses

C. Epithelial defects

D. Microbiota (the microorganisms of a particular site, here; the intestine.)
Genetic factors

- Risk of IBD increases if there is a family member affected.

- Concordance rate with monozygotic twins: 50% in Crohn’s and 16% in ulcerative colitis.

- This shows that there are genetic factors important in the development of IBD.

- Obviously these factors are more prominent in Crohn’s disease.
• So: people developing IBD, must have certain gene abnormalities or polymorphisms that make them susceptible to develop the disease.

• there are three important genes that are thought to play a role in this: **NOD 2, ATG 16L1, IRGM.**

• *Polymorphisms of these genes are seen in Crohn’s disease but not in Ulcerative colitis.*
NOD 2

- = nucleotide oligomerization binding domain

- Also known as IBD 1… see how easy life can be!

- NOD 2 mutations are found in Crohn disease but not Ulcerative colitis (UC)

- NOD 2 is important in inflammation and immune function.

- It actually acts as a **pattern recognition receptor** which recognises microbial components and elicits an immune and inflammatory reaction against these microbes. So if this receptor is normal microbes will be recognised and defeated in the intestinal lumen or superficial mucosa before they penetrate deeper into lamina propria.

- People with mutated NOD have a defect in recognising microbes so these microbes can enter lamina propria and elicit an inflammatory response.

- **Note**: only 10% of people with NOD 2 mutation develop Crohn disease.
Pattern recognition receptors/ a quick reminder

• these are receptors that recognise microbes or products of cell injury.

• they recognise patterns of molecules, not a specific molecular sequence.

• toll like receptors and NOD are part of this family.
Pattern recognition receptors (PRRs) may be soluble or bound to a host cell.
ATG 16 L1

• = Autophagy related 16 like 1

• Part of the autophagy pathway, a process important in response to intracellular bacteria.

• Remember that in autophagy the cell uses its own lysosomal enzymes to phagocytose parts of its own components and organelles. This process can be beneficial in getting rid of intracellular microbes (they become part of the meal for the lysosomes!)
IRGM

- Immunity related GTPase M
- Also involved in autophagy and clearance of intracellular bacteria
Recap

Don’t be lost in the details, the issue is so easy:

• for IBD to occur we need genetic susceptibility.

• The genetic changes are better known for Crohn but not yet discovered for UC

• the main genetic polymorphisms related to Crohn’s are in genes related to regulating inflammatory and immune responses to microbes.

• these include a mutation in a pattern recognition receptor (NOD 2) and in genes regulating autophagy (don't worry about the stupid names, if you need them Uncle Google is always there to remind you)
Abnormal mucosal immune responses

- IBD is treated by immunosuppressive therapy, which indicates that immune responses play a role in its pathogenesis.

- The exact mechanism are not fully understood, but in Crohn the T helpers differentiate to certain subtypes (Th 1 and Th 17) and this is thought to play a role in increased immune response to pathogens.

- This maturation is regulated by polymorphisms in cytokines that trigger the differentiation.
One model of IBD pathogenesis. Aspects of both CD and UC.
Epithelial defects

- people with IBD are found to have defective epithelium, this probably allows bacterial entry to the epithelium.

- Known defects include: defective tight junctions and defective paneth cell granules.
Microbes can enter through defects in tight junctions
Paneth cell granules contain antimicrobial peptides. These can be defective in IBD.
Microbiota

• we have a huge amount of microorganisms in our GI tract.

• this flora (microbiota) is different between individuals; it is modified by food and infections.

• it is thought that the composition of this flora affects IBD, but the mechanism is not well understood.

• Evidence: antibiotics can help in maintaining disease remission. And changing microbiota is now investigated as a possible treatment for IBD not responding to treatment.
Faecal microbiota transplantation: stool from healthy individual filtered and administered through enema or other routes to change the microbiota of IBD patients. This is an experimental treatment but research shows promising results.
So: IBD occurs as a combination of the previously mentioned mechanisms.
• The pathogenesis we detailed is common to Crohn and UC.

• so why we are considering these as two diseases?

• because *they differ* in their clinical presentation, distribution in the GI tract, histological features, risk of malignancy and other features.
Crohn’s disease

- Americans call this Crohn, British prefer keeping the apostrophe (Crohn’s).. as usual the British are correct!

- Crohn’s disease affects any part of the GI tract, in a non-continuous fashion, so some areas are affected and adjacent areas are normal. The inflammation affects all layers of the intestine in the affected areas (from the mucosa to the serosa); this is called transmural inflammation.
Note that Crohn’s causes transmural inflammation, whereas UC affects the mucosa only.
Crohn disease

• Presents with diarrhoea, fever and abdominal pain.

• the symptoms come and go, the medical term for come and go is: relapsing - remitting.

• Relapses of symptoms might be associated with environmental triggers like stress, certain foods, smoking.

• Crohn can affect any part of the GI tract. if small bowel affected patients might have malabsorption and if large bowel affected anaemia might occur due to bloody diarrhoea

• Strictures can occur due to the inflammation.
• Complications of Crohn include: strictures, fistulas, perforation.

• Extra-intestinal manifestations might occur and include uveitis, migratory polyarthritis, ankylosing spondylitis (arthritis affecting the spine), erythema nodosum, finger clubbing.

• Primary sclerosis cholangitis might occur but less often than in UC
Finger clubbing: one of the extra-intestinal manifestations of Crohn disease.
Erythema nodosum: red patches mainly on the anterior of the legs.
Crohn's disease

- Eye inflammation
- Mount ulcer
- Skin ulcers and sores
- Stomatitis
- Liver and bile duct inflammation
- Intestinal diarrhea, abdominal pain, cramping, ulcers in digestive tract
- Rectal bleeding
- Stomach vomiting
- Joint pain and swelling
- Fever, weight loss, decreased appetite
Morphology of Crohn disease

- Crohn affects any part of the GI
- Can be limited to small intestine, limited to large intestine or might affect both.
Crohn might affect any part of the GI. Involvement can affect some parts and leave others normal in the patient, the affected parts are called skip areas.
Skip lesions: means abnormal (inflamed) areas adjacent to normal mucosa. This occurs in Crohn but not UC.
• Patients have small ulcers = aphthous ulcers.

• With time these might form larger ulcers

• Deep ulceration might also occur.

• Because the disease is not continuous, inflamed mucosa is depressed while adjacent normal mucosa is unaffected, this creates a rough texture called cobblestone appearance. see next slide.

• Intestinal wall is thickened due to the transmural inflammation.
Cobblestone appearance
Microscopic appearance

- Patients have increased inflammatory cells in the affected areas.
- These are mainly neutrophils.
- The neutrophils are seen in the lamina propria, and in the crypts (intestinal glands).
- If neutrophils are attacking the wall of the gland = cryptitis.
- If they enter the lumen of the gland = crypt abscess.
Cryptitis = neutrophils invading the wall of the crypt (gland)
Crypt abscess: neutrophils within the crypt
• the cryptitis and crypt abscesses mean the inflammation is active, so the patient has a relapse of his symptoms.

• we said the disease is relapsing remitting, so patients will have cycles of inflammation and repair.

• with repeated attacks, and with repair process the crypts become abnormal in shape.

• this abnormality is usually seen as irregular branched glands.
Normal colonic glands (crypts) are rounded, and contain goblet cells, they look like daisy flowers. In Crohn’s this architecture is lost and distorted.
Distorted architecture of colonic crypts. this occurs due to cycles of inflammation and repair, it means the disease is chronic.
Check how irregular these glands are!
Granulomas

- *another feature of Crohn’s, which is never seen in UC, is the presence of granulomas.*

- Of course these granulomas are non-caseating... remember that caseating granulomas are seen in tuberculosis.

- Granulomas are seen in 35% of Crohn’s cases.

- they can be seen anywhere in the GI tract and in any layer of the intestine.
Granulomas in Crohn’s
Another granuloma.
Ulcerative colitis

- UC is limited to the colon and rectum. It doesn't affect the small intestine.

- It always starts in the rectum and affects variable lengths of the large bowel in a continuous fashion. There are no skip lesions.
Note that the disease is continuous, there are no skip lesions.

TYPES OF ULCERATIVE COLITIS
CROHN DISEASE

Skip lesions

ULCERATIVE COLITIS

Continuous colonic involvement, beginning in rectum
Clinical picture

- Remitting- relapsig
- Bloody diarrhoea and abdominal pain
- Extra intestinal manifestation similar to Crohn’s.
- primary sclerosing cholangitis commoner in UC than in Crohn’s.
- With severe symptoms surgery might be needed
- NOTE: colectomy cures the intestinal symptoms but extra intestinal manifestations might persist after colectomy.
Morphology

• The mucosa appears red and ulcerations might occur.

• The inflammation in UC is limited to the mucosa, so the serosa is normal and there is no thickening like that seen in Crohn disease.

• No fissures or fistulas .. because the inflammation is superficial.
Histology

- Similar to Crohn’s: cryptitis, crypt abscesses and branching and irregularity.

- However: there are no granulomas and the inflammation is limited to the mucosa and sometimes superficial submucosa.
Complications

- the inflammation and inflammatory mediators can damage the neuromuscular function leading to dilated colon = toxic megacolon.

- Toxic megacolon has a high risk of rupture.
Risk of malignant transformation in IBD

- In UC there is risk of malignant transformation
- in Crohn’s there is risk if the large bowel is involved.
## COMPARISON

<table>
<thead>
<tr>
<th>Feature</th>
<th>Crohn Disease</th>
<th>Ulcerative Colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Macroscopic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bowel region affected</td>
<td>Ileum ± colon</td>
<td>Colon only</td>
</tr>
<tr>
<td>Rectal involvement</td>
<td>Sometimes</td>
<td>Always</td>
</tr>
<tr>
<td>Distribution</td>
<td>Skip lesions</td>
<td>Diffuse</td>
</tr>
<tr>
<td>Stricture</td>
<td>Yes</td>
<td>Rare</td>
</tr>
<tr>
<td>Bowel wall appearance</td>
<td>Thick</td>
<td>Thin</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Transmural</td>
<td>Limited to mucosa and submucosa</td>
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</tbody>
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Thank you!