GIT pathology Lec. 3

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SMALL & LARGE INTESTINE
Several pathological conditions, such as infections, inflammatory diseases, motility disorders, and tumors, affect both the small and large intestines simultaneously. These two organs will therefore be considered together.
CONGENITAL ANOMALIES

Anomalies of the intestine are rarely encountered; these include duplication of the small intestine or colon; malrotation of the entire bowel; omphalocele (birth of an infant with herniation of abdominal contents into a ventral membranous sac related to umbilicus); heterotopía of pancreatic tissue or gastric mucosa; atresia and stenosis; imperforated anus.
Congenital Aganglionic Megacolon (Hirschsprung Disease):
This congenital disorder is characterized by the absence of ganglia of the submucosal and myenteric neural plexuses, within a portion of the intestinal tract. The outcome is contraction and functional obstruction of the aganglionic segment with secondary proximal dilation. The rectum is always affected and most cases involve the rectum and sigmoid colon only (short-segment disease). In some cases longer segments, and rarely the entire colon may be aganglionic (long-segment disease).
Normal sigmoid colon and rectum

Area affected by Hirschsprung’s disease
Proximal to the aganglionic segment, the ganglionic colon undergoes progressive dilation and hypertrophy, sometimes massively (megacolon). When distention over runs hypertrophy, the colonic wall becomes markedly thinned and may rupture.
Diagnosis of Hirschsprung is made histologically by failure to detect ganglion cells in intestinal biopsy samples of the contracted (agnaglionic) segment. The disease usually manifests itself in the immediate neonatal period by failure to pass meconium, followed by obstructive constipation. Abdominal distention may secondarily develop. The major threats to life are superimposed enterocolitis with fluid and electrolyte disturbances and perforation with peritonitis.
ENTEROCOLITIS

These are divided into three etiological categories

I. Infectious (caused by microbiologic agents)
II. Malabsorption-associated
III. Idiopathic inflammatory bowel diseases
INFECTIOUS ENTEROCOLITIS
This is the cause of more than 12,000 deaths per day among children in developing countries, and constituting 50% of all deaths before the age of 5 years worldwide. Acute, self-limited infectious diarrhea is most frequently caused by enteric viruses (such as rotavirus and adenoviruses). Bacterial infections, such as that caused by enterotoxigenic Escherichia coli, are also common. In up to 50% of cases, the specific agent cannot be isolated.
Viral enterocolitis
The lesions caused by enteric viruses in the intestinal tract are similar. The small intestinal mucosa shows partial villous atrophy (shortening of the villi) with infiltration of the lamina propria by lymphocytes. However, in infants, rotavirus and adenoviruses can produce total villous atrophy (flat mucosa), thus resembling celiac disease (see later).
BACTERIAL ENTEROCOLITIS
Salmonellosis
Campylobacter Enterocolitis
Cholera
Antibiotic-Associated Colitis (Pseudomembranous Colitis)

Tuberculous enteritis
Intestinal tuberculosis contracted by the drinking of contaminated milk was common as a primary focus of the disease. In developed countries today, intestinal tuberculosis is more often a complication of advanced pulmonary tuberculosis i.e. secondary to the swallowing of coughed-up infective sputum.
General pathological features of bacterial enteric diseases

- These are quite variable.
- Dramatic, even lethal, diarrhea may occur without a significant pathologic lesion, as in cholera.
- Characteristic histology may enable diagnosis with reasonable certainty, as with *C. difficile*-induced pseudomembranous colitis, and caseating granulomas of TB.
THE MALABSORPTION SYNDROMES

Malabsorption is characterized by defective absorption of fats, fat-soluble and other vitamins, proteins, carbohydrates, electrolytes and minerals, and water. The most common clinical presentation is chronic diarrhea, and the hallmark of malabsorption is steatorrhea (excessive fecal fat content). Although many causes of malabsorption can be established clinically, small intestinal mucosal biopsy may be required to satisfactorily identify or exclude celiac disease.
Major Malabsorption Syndromes

Clinically, the malabsorption syndromes resemble each other more than they differ. The consequences of malabsorption affect many organ systems. The passage of abnormally bulky, frothy, greasy, yellow, or gray stools (steatorrhea) is a prominent feature of malabsorption; this is accompanied by weight loss, abdominal distention, and muscle wasting.
The malabsorptive disorders most commonly encountered are:

1. Celiac disease
2. Pancreatic insufficiency
Pancreatic insufficiency
Primarily from chronic pancreatitis or cystic fibrosis, is a major cause of defective intraluminal digestion that leads to diarrhea and steatorrhea.

Celiac Disease
Celiac disease (gluten-sensitive enteropathy, GSE) is a chronic disease, in which there is a characteristic mucosal lesion of the small intestine and impaired nutrient absorption, which improves on withdrawal of wheat gluten from the diet.
Pathogenesis

- The fundamental disorder in celiac disease is sensitivity to gluten component called gliadin, which is a protein present in wheat and closely related grains (e.g. oat).

- There is a T-cell mediated chronic inflammatory reaction, which develops as a consequence of a loss of tolerance to gluten.
Interplay between genetic predisposing factors, the host immune response, and environmental factors, is central to disease pathogenesis.

The small intestinal mucosa, when exposed to gluten, accumulates intraepithelial CD8+ T cells and large numbers of lamina propria CD4+ T cells, which are sensitized to gliadin.

Gliadin is deamidated by the enzyme transglutaminase; the resultant peptides are recognized by CD4+ T cells. This leads to secretion of interferon γ, which damages enterocytes.
The left panel illustrates the morphologic alterations that may be present in celiac disease, including villous atrophy, increased numbers of intraepithelial lymphocytes (IELs), and epithelial proliferation with crypt elongation. The right panel depicts a model for the pathogenesis of celiac disease. Note that both innate and adaptive immune mechanisms are involved in the tissue responses to gliadin.
Pathological features:

- By endoscopy, the duodenal mucosa appears flat (normally shows mucosal folds).
- Biopsies demonstrate enteritis with partial or total loss of villi (partial villous atrophy or completely flat mucosa respectively).
- The surface epithelium shows degeneration, loss of the microvillus brush border, and an increased number of intraepithelial lymphocytes.
- The crypts exhibit increased mitotic activity and are hyperplastic, so that, despite villous atrophy, the overall mucosal thickness remains the same.
The lamina propria has an overall increase in plasma cells and lymphocytes.

Although the above changes are characteristic of celiac disease, they can be mimicked by other diseases, most notably tropical sprue.

Mucosal histology usually reverts to normal or near-normal following gluten exclusion from the diet.
Definitive diagnosis of celiac disease rests on:

1. clinical documentation of malabsorption
2. demonstration of the intestinal lesions by small bowel biopsy.
3. Definite improvement in both symptoms and mucosal histology on gluten withdrawal from the diet.
4. If there is doubt about the diagnosis, gluten challenge (reintroduction of gluten to the diet) followed by re-biopsy has been advocated.
5. Serologic tests, mentioned above, are used for screening or treatment follow-up.
Most patients with celiac disease who adhere to a gluten-free diet remain well indefinitely and ultimately die of unrelated causes. However, there is a long-term risk of malignant disease, which includes small intestinal non-Hodgkin lymphoma (moderate risk), small intestinal adenocarcinoma, and esophageal squamous cell carcinoma (50- to 100-fold higher risk than the general population).
IDIOPATHIC INFLAMMATORY BOWEL DISEASE (IBD)
The two disorders known as inflammatory bowel disease (IBD) are Crohn's disease (CD) and ulcerative colitis (UC). These diseases have distinctly different clinical and pathological features. Both CD and UC are chronic, relapsing inflammatory disorders of obscure origin. CD is an autoimmune disease that may affect any portion of the gastrointestinal tract from mouth to anus, but most often involves the distal small intestine and colon. UC is a chronic inflammatory disease limited to the rectum and colon. Both exhibit extra-intestinal inflammatory manifestations
Etiology and Pathogenesis

In the normal GIT, the mucosal immune system is always ready to respond against ingested pathogens but is unresponsive to normal intestinal microflora. In IBD, this state of homeostasis is disrupted, leading to two key pathogenic abnormalities

1. Strong immune responses against normal microflora
2. Defects in epithelial barrier that cause microflora to reach the lymphoid tissue of the intestine
The exact cause(s) leading to the above is still not established, hence the designation idiopathic. It is postulated that IBD result from exaggerated local immune responses to microflora in the gut, in genetically susceptible individuals. Thus, the pathogenesis of IBD involves:

1. Failure of immune regulation
2. Genetic susceptibility
3. Environmental triggers specifically microbial flora.

CD appears to be the result of a chronic delayed-type hypersensitivity reaction induced by IFN-γ-producing TH1 cells. This is supported by the presence of granulomas in this disease. Experiments on animals suggest that UC is caused by excessive activation of TH2 cells.
Crohn Disease (CD)

This disease may involve any level of the alimentary tract. CD occurs at any age, but the peak age of incidence is between 10 and 30 years. Smoking has been found to be a strong risk factor.

Pathological features

When fully developed, Crohn disease is characterized pathologically by

1. Sharply segmental and typically transmural involvement of the bowel by an inflammatory process with mucosal damage

2. The presence of
   - Small noncaseating granulomas
   - Deep fissures that may eventuate in the formation of fistulae
In CD, there is involvement of the small intestine alone in about 40% of cases, of small intestine and colon in 30%, and of the colon alone in about 30%. Other portions of the GIT may also be uncommonly involved.
Gross features:

- Segments of the small bowel involved by the disease show granular and dull gray serosa (normally transparent and glistening).
- Often the mesenteric fat wraps around the bowel (creeping fat).
- The involved bowel wall is thick and rubbery (because of edema, inflammation, and fibrosis). As a result, the lumen is narrowed.
- A classic feature of CD is the sharp demarcation of diseased bowel segments from adjacent uninvolved, essentially normal bowel (skip lesions).
- Early disease shows small mucosal ulcers that coalesce to form long, serpentine linear ulcers (i.e. long and twisted or sinuous).
As the intervening mucosa (between the ulcers) tends to be accentuated by inflammation and edema, it acquires a cobblestone appearance. (Cobble-stone, is a rounded stone, esp. of the size used for paving).

Narrow fissures develop between the mucosal folds, often penetrating deeply through the bowel wall. Further extension of these fissures leads to fistulae or sinus tracts formation, between the diseased intestinal segment and adherent structures (bowel loops, vagina, urinary bladder, skin of the abdomen) or the sinuses may end blindly within the abdominal cavity.

Free perforation or localized abscesses may develop.
Cobblestone appearance of mucosal surface due to linear ulceration

Narrowed lumen
Thickened wall
Normal portion of intestine
Abcess
Microscopic features:

The characteristic histologic features of CD are:

1. Acute mucosal inflammation: there is neutrophilic infiltration of the surface & crypt epithelium that eventually collects within the lumen of the crypts forming crypt abscesses.

2. Chronic mucosal damage:

This is the hallmark of chronicity of CD (and UC). It manifests as architectural distortion (in the small intestine as villus blunting; in the colon, the crypts exhibit irregularity, and branching). Crypt destruction leads to progressive mucosal atrophy.
3. Ulcerations are the usual outcome of severe active disease; these may be superficial, or may penetrate deeply (as fissures) into underlying tissue layers.

4. Transmural chronic inflammation affecting all layers: chronic inflammatory cells (lymphocytes and plasma cells) fill the affected mucosa and, to a lesser extent, all underlying intestinal layers. Lymphoid aggregates are usually scattered throughout the bowel wall.

5. Noncaseating granulomas: in about 50% of the cases, noncaseating small granulomas may be present in all tissue layers. Because they are not always present; the absence of granulomas does not rule out the diagnosis of CD.
6. Other mural changes: in diseased segments, the muscularis mucosae usually exhibits duplication & thickening. There is also fibrosis of the submucosa, muscularis propria, and serosa that eventually leads to stricture formation.

7. Dysplastic changes of the mucosal epithelial cells are particularly important in persons with long-standing chronic disease are. These may be focal or widespread, tend to increase with time, and are thought to be related to increased risk of carcinoma, particularly of the colon.
ULCERATIVE COLITIS

In contradistinction to CD, ulcerative colitis is a chronic ulcerone-inflammatory disease limited to the colon and affecting only the mucosa and submucosa; it extends in a continuous fashion proximally from the rectum. Well-formed granulomas are absent. However, like CD, UC is a systemic disorder associated in some patients with arthritis, uveitis, hepatic involvement (primary sclerosing cholangitis), and skin lesions. The onset of disease peaks between ages 20 and 25 years. Nonsmoking is associated with UC; ex-smokers are at higher risk for developing UC than never-smokers.
Healthy Colon

Ulcerative Colon
Pathological features

Ulcerative colitis involves the rectum and extends proximally in a retrograde fashion to involve the entire colon ("pancolitis") in the more severe cases. It is a disease of continuity, and "skip" lesions are not found.
Gross features:

- A key feature of UC is that the mucosal damage is continuous from the rectum and extending proximally.
- The mucosa may exhibit reddening and granularity with easy bleeding.
- With fully developed severe, active inflammation, there may be extensive ulcerations of the mucosa.
- Isolated islands of regenerating mucosa bulge upward to create polypoid projections (pseudopolyps).
- With chronicity or healing of active disease, progressive mucosal atrophy occurs.
- Thickening of the bowel wall does not occur in UC; the serosal surface is usually completely normal (cf. CD).
- Only in the most severe cases of ulcerative disease (UC, CD, and other severe inflammatory diseases) does toxic damage to the muscularis propria and neural plexus lead to complete shutdown of neuromuscular function. In this instance the colon progressively swells and becomes gangrenous, a life-threatening condition called toxic megacolon.
Microscopic features:

- The basic mucosal alterations in UC are similar to those of colonic CD, with inflammation, chronic mucosal damage, and ulceration.
- There is diffuse, predominantly chronic inflammatory infiltrate in the lamina propria.
- Neutrophilic infiltration of the epithelial layer may produce crypt abscesses. The latter are not specific for UC and may be observed in CD or any active inflammatory colitis.
- Unlike CD, there are no granulomas.
Destruction of the mucosa leads to broad-based ulcerations that are superficial i.e. extending at most into the submucosa.

Isolated islands of regenerating mucosa bulge upward to create pseudopolyps.

Features of chronic but healed (inactive) disease include submucosal fibrosis; mucosal architectural distortion and atrophy.

Particularly significant is the spectrum of epithelial dysplasias, which are divided into low-grade and high-grade depending on the severity. Invasive carcinoma is the ultimate lesion arising from dysplasia.
Continuous colonic involvement, beginning in rectum

Active disease: superficial ulceration

AND/OR

Inactive disease: atrophy

Large intestine
To summarize UC differs pathologically from CD in the following

a. Well-formed granulomas are absent.

b. There are no skip lesions.

c. The mucosal ulcers rarely extend below the submucosa, and

d. There is surprisingly little fibrosis.

e. Mural thickening does not occur, and the serosal surface is usually completely normal.

f. There appears to be a higher risk of carcinoma development
Course & prognosis
Ulcerative colitis typically presents as a recurrent attacks of bloody mucoid diarrhea that may persist for days, weeks, or months and then subside, only to recur after an asymptomatic interval of months to years.
The outcome of UC depends on two factors:
1. The severity of active disease
2. The duration of the disease
The majority of the cases can be controlled medically; however, about 30% of patients require colectomy due to uncontrollable active disease. On rare occasion, the disease runs a fulminant course; unless medically or surgically controlled, this toxic form of the disease can lead to death soon after onset.

The most serious long-term complication of UC is colonic carcinoma. There is a tendency for dysplasia to arise in multiple sites. The associated carcinomas are often infiltrative without obvious exophytic masses. Historically, the risk of cancer is highest in patients with pancolitis of 10 or more years' duration. It is believed that with 10 years of disease limited to the left colon the risk is minimal, and at 20 years the risk is on the order of 2%. With pancolitis, the risk of carcinoma is 10% at 20 years and up to 25% by 30 years. Overall, the annual incidence of colon cancer in persons with ulcerative colitis of more than 10 years' duration is 1%.