Small and Large Intestinal pathology, part 3

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Diseases of the intestines

- Intestinal obstruction
- Vascular disorders
- Malabsorptive diseases and infections
- Inflammatory bowel disease.
- **Polyps and neoplastic diseases**
COLONIC POLYPS AND NEOPLASTIC DISEASE

- Colon is most common site for polyps
- *Sessile polyp*: no stalk
- *Pedunculated polyp*: stalk.

- *Neoplastic polyps*: adenoma.
- *Non neoplastic polyps*: inflammatory, hamartomatous, or hyperplastic
Inflammatory Polyps

- *Solitary rectal ulcer syndrome.*
- Recurrent abrasion and ulceration of the overlying rectal mucosa.
- Chronic cycles of injury and healing give a polypoid mass of inflamed and reactive mucosal tissue.
Hamartomatous Polyps

- Sporadic or syndromatic.
- Disorganized, tumor-like growth composed of mature cell types normally present at that site.

- Juvenile Polyps
- Peutz-Jeghers Syndrome
Juvenile Polyps

- Most common hamartomatous polyp

- **Sporadic are solitary.**
  - Children younger than 5 years of age
  - Rectum.

- **Syndromic are multiple.**
  - 3 to as many as 100. Mean age 5 years
  - Autosomal dominant syndrome of juvenile polyposis
  - Transforming growth factor-β (TGF-β) mutation.
  - Increased risk for colonic adenocarcinoma.
Juvenile Polyps

- Pedunculated
- Reddish lesions
- Cystic spaces on cut sections
- Dilated glands filled with mucin and inflammatory debris.
- Granulation tissue on surface.
Peutz-Jeghers Syndrome

- Autosomal dominant, rare
- Mean age: 10-15 years.
- Multiple gastrointestinal hamartomatous polyps
- Most common in the small intestine.
- Mucocutaneous hyperpigmentation
- Increased risk for several malignancies: colon, pancreas, breast, lung, ovaries, uterus, and testes,

- LKB1/STK11 gene mutation.
Peutz-Jeghers polyp

- Large.
- Arborizing network of connective tissue, smooth muscle, lamina propria
- Glands lined by normal-appearing intestinal epithelium
- Christmas tree pattern.
Hyperplastic Polyps

- Common
- 5th-6th decade.
- Decreased epithelial turnover and delayed shedding of surface epithelium >>> pileup of goblet cells & epithelial overcrowding
- No malignant potential
Hyperplastic polyp

- Left colon
- Rectosigmoid.
- Small < 5 mm
- Multiple

- Crowding of goblet & absorptive cells.
- Serrated surface: hallmark of these lesions
Adenomas

- Most common and clinically important
- *Increase with age.*
- *Definition: presence of epithelial dysplasia (low or high).*
- Precursor for majority of colorectal adenocarcinomas
- *Most adenomas DO NOT progress to carcinoma.*
- *USA: screening colonoscopy starts at 50 yrs.*
- *Earlier screening with family history.*
- *Western diets and lifestyles increase risk.*
Pedunculated or sessile
Colon adenoma

- **Hallmark:** epithelial dysplasia
- **Dysplasia:** nuclear hyperchromasia, elongation, stratification, high N/C ratio.
- **Size:** most important correlate with risk for malignancy
- **High-grade dysplasia** is the second factor
Tubular adenoma
Villous adenoma.

- Long slender villi.
- More frequent invasive foci

**Architecture:**
- Tubular.
- Tubulovillous.
- Villous.
Villous adenoma
Familial Syndromes

- Syndromes associated with colonic polyps and increased rates of colon cancer
- Genetic basis.

- Familial Adenomatous Polyps (FAP)
- Hereditary Nonpolyposis Colorectal Cancer (HNPCC)
Familial adenomatous polyposis FAP

- Autosomal dominant.
- Numerous colorectal adenomas: teenage years.
- Mutation in APC gene.
- At least 100 polyps are necessary for a diagnosis of classic FAP.
- Morphologically similar to sporadic adenomas
- 100% of patients develop colorectal carcinoma, if untreated, often before age of 30.
- Standard therapy: prophylactic colectomy before 20 Year of age.
- Risk for extraintestinal manifestations,
Variants of FAP: Gardner syndrome and Turcot syndrome.

**Gardner syndrome:** intestinal polyps + osteomas (mandible, skull, and long bones); epidermal cysts; desmoid and thyroid tumors; and dental abnormalities.

**Turcot syndrome:** intestinal adenomas and CNS tumors (medulloblastomas >> glioblastomas)
Hereditary Nonpolyposis Colorectal Cancer: HNPCC, Lynch syndrome

- Clustering of tumors: Colorectum, endometrium, stomach, ovary, ureters, brain, small bowel, hepatobiliary tract, and skin
- Colon cancer at younger age than sporadic cancers
- Right colon with excessive mucin production.
- Adenomas are present, BUT POLYPOSIS IS NOT.

- Inherited germ line mutations in DNA mismatch repair genes.
- Accumulation of mutations in microsatellite DNA (short repeating sequences)
- Resulting in microsatellite instability
- Majority of cases involve either MSH2 or MLH1.
Cecal polyps in HNPCC.
Colonic Adenocarcinoma

- Most common malignancy of the gastrointestinal tract
- Small intestine is uncommonly involved by neoplasia.
- Peak: 60 to 70 years
- 20% under 50 years.
- Developed countries lifestyles and diet.
- Low intake of vegetable fiber and high intake of carbohydrates and fat.
- Aspirin or other NSAIDs have a protective effect.
- Cyclooxygenase-2 (COX-2) promotes epithelial proliferation.
Pathogenesis

- Heterogeneous molecular events.
- Sporadic >>> familial.
- Two pathways:
  - APC/β-catenin pathway >> increased WNT signaling
  - Microsatellite instability pathway >> defects in DNA mismatch repair
- Stepwise accumulation of multiple mutations
The APC/β-catenin pathway: chromosomal instability

- Classic adenoma carcinoma sequence.
- 80% of sporadic colon tumors
- Mutation of the APC tumor suppressor gene: EARLY EVENT
- APC is a key negative regulator of β-catenin, a component of the WNT signaling pathway.
- Both copies of APC should be inactivated for adenoma to develop (1\textsuperscript{st} and 2\textsuperscript{nd} hits).
- Loss of APC >>> accumulation of B-catenin >> enters nucleus >> MYC and cyclin-D1 transcription >> promote proliferation.
- Additional mutations >> activation of KRAS (LATE EVENT) >> inhibits apoptosis.
- SMAD2 and SMAD4 mutations (tumor suppressor genes.)

- TP53 is mutated in 70% -80% of colon cancers (LATE EVENT IN INVASIVE)
- TP53 inactivation mutation
- Expression of telomerase also increases as the tumor advances.
NORMAL COLON

MUCOSA AT RISK

ADENOMAS

CARCINOMA

Germline (inherited) or somatic (acquired) mutations of cancer suppressor genes ("first hit")

Methylation abnormalities Inactivation of normal alleles ("second hit")

Protooncogene mutations

Homozygous loss of additional cancer suppressor genes Overexpression of COX-2

Additional mutations Gross chromosomal alterations

Mucosa

Submucosa

Muscularis propria

APC at 5q21

APC β-catenin

K-RAS at 12p12

TP53 at 17p13

LOH at 18q21 (SMAD 2 and 4)

Telomerase, Many genes
The microsatellite instability pathway

- DNA mismatch repair deficiency
- Loss of mismatch repair genes
- Mutations accumulate in microsatellite repeats
- Microsatellite instability

- Silent if microsatellites located in noncoding regions
- Uncontrolled cell growth if located in coding or promoter regions of genes involved in cell growth and apoptosis (TGF-B and BAX genes)
NORMAL COLON

Mucosa
Submucosa
Muscularis propria

Germline (inherited) or somatic (acquired) mutations of mismatch repair genes

ALTERATION OF SECOND ALLELE BY LOH, MUTATION, OR PROMOTER METHYLATION

SESSILE SERRATED ADENOMA

Microsatellite instability / "mutator phenotype"

CARCINOMA

Accumulated mutations in genes that regulate growth, differentiation, and/or apoptosis

MLH1, MSH2
(MSH6, PMS1, PMS2)

TGFβRII, BAX, BRAF, TCF-4, IGF2R, others
<table>
<thead>
<tr>
<th>Etiology</th>
<th>Molecular Defect</th>
<th>Target Gene(s)</th>
<th>Transmission</th>
<th>Predominant Site(s)</th>
<th>Histology</th>
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</thead>
<tbody>
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<td>Familial adenomatous polyposis (70% of FAP)</td>
<td>APC/WNT pathway</td>
<td>APC</td>
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<td>Tubular, villous; typical adenocarcinoma</td>
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MORPHOLOGY

- Proximal colon tumors: polypoid, exophytic masses
- Proximal colon: rarely cause obstruction.
- Distal colon: annular lesions “napkin ring” constrictions & narrowing
- Tall columnar cells of dysplastic epithelium forming GLANDS with strong desmoplastic response.
- Necrotic debris are typical.
- Some tumors give abundant mucin.
- Some form signet ring cells.
Rectosigmoid adenocarcinoma, napkin ring
Exophytic adenocarcinoma
Adenocarcinoma with necrosis
Clinical Features

- Endoscopic screening >> cancer prevention
- Early cancer is asymptomatic !!!!!!!!
- Cecal and right side cancers: Fatigue and weakness (iron deficiency anemia)
- Iron-deficiency anemia in an older male or postmenopausal female is gastrointestinal cancer until proven otherwise.

- Left sided carcinomas: occult bleeding, changes in bowel habits, cramping left lower-quadrant discomfort.
Poor differentiation and mucinous histology >> poor prognosis

Most important two prognostic factors are
- **Depth of invasion**
- **Lymph node metastasis.**

- **Distant metastases (lung and liver) can be resected.**
Liver metastasis.
Appendix

- Normal true diverticulum of the cecum
- ACUTE APPENDICITIS
- TUMORS OF THE APPENDIX
ACUTE APPENDICITIS

- Most common in adolescents and young adults.
- May occur in any age.
- Difficult to confirm preoperatively

DDx:
- Mesenteric lymphadenitis,
- Acute salpingitis,
- Ectopic pregnancy,
- Mittelschmerz (pain associated with ovulation),
- Meckel diverticulitis.
Luminal obstruction in 50-80% of cases >> increased luminal pressure >> impaired venous drainage >> ischemic injury & stasis associated bacterial proliferation >>> inflammatory response rich in neutrophils & edema.

Obstruction by fecalith, less commonly: gallstone, tumor, worms....

Diagnosis requires neutrophilic infiltration of the muscularis propria

Acute suppurative appendicitis >> more severe >> focal abscess formation.

Acute gangrenous appendicitis >> necrosis and ulceration.
Clinical Features

- Early acute appendicitis: periumbilical pain
- Later: pain localizes to the right lower quadrant,
- Nausea, vomiting, low-grade fever, mildly leukocytosis.
- A classic physical finding is McBurney’s sign (McBurney’s point).
- Signs and symptoms are often absent, creating difficulty in clinical diagnosis.
TUMORS OF THE APPENDIX

- The most common tumor: carcinoid (neuroendocrine tumor)
- Incidentally found during surgery or on examination of a resected appendix
- Distal tip of the appendix
- Nodal metastases & distant spread are rare.
Carcinoid tumor

Gross

Microscopic