GIT III

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Polyps

- Most common in the colon but may occur in the esophagus, stomach, or small intestine
- Sessile
- Pedunculated
Intestinal polyps

Non-neoplastic
- Inflammatory
- Hamartomatous
- Hyperplastic

Neoplastic
- Adenomatous
- Sessile serrated polyp
INFLAMMATORY POLYPS

• Purely inflammatory lesion
• Example: solitary rectal ulcer
• Result of chronic cycles of injury and healing.

**Fig. 11.119 A and B**, Gross appearance of inflammatory fibroid polyp.
HAMARTOMATOUS POLYPS

• Sporadically
• Genetically determined or acquired syndromes
• Recall that hamartomas are tumor-like growths composed of mature tissues that are normally present at the site in which they develop.
• Although hamartomatous polyposis syndromes are rare, they are important to recognize because of associated intestinal and extra-intestinal manifestations and the possibility that other family members are affected.
# Familial hamartomatous polyposis

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Mean Age</th>
<th>Mutated Gene</th>
<th>Gastrointestinal Lesions</th>
<th>Selected Extra-Gastrointestinal Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td>10–15</td>
<td>LKB1/STK11</td>
<td>Arborizing polyps; Small intestine &gt; colon &gt; stomach; colonic adenocarcinoma</td>
<td>Skin macules; increased risk of thyroid, breast, lung, pancreas, gonadal, and bladder cancers</td>
</tr>
<tr>
<td>Juvenile polyposis</td>
<td>&lt;5</td>
<td>SMAD4, BMPR1A</td>
<td>Juvenile polyps; risk of gastric, small intestinal, colonic, and pancreatic adenocarcinoma</td>
<td>Pulmonary arteriovenous malformations, digital clubbing</td>
</tr>
<tr>
<td>Cowden syndrome, Bannayan-Ruvalcaba-Riley syndrome</td>
<td>&lt;15</td>
<td>PTEN</td>
<td>Hamartomatous polyps, lipomas, ganglioneuromas, inflammatory polyps, risk of colon cancer</td>
<td>Benign skin tumors, benign and malignant thyroid and breast lesions</td>
</tr>
</tbody>
</table>
## Familial hamartomatous polyposis

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Age of Onset</th>
<th>Inheritance</th>
<th>Main Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cronkhite-Canada Syndrome</td>
<td>&gt;50</td>
<td>Nonhereditary</td>
<td>Hamartomatous colon polyps, crypt dilatation and edema in nonpolypoid mucosa, Nail atrophy, hair loss, abnormal skin pigmentation, cachexia, and anemia</td>
</tr>
<tr>
<td>Tuberous Sclerosis</td>
<td>TSC1, TSC2</td>
<td>Hamartomatous polyps (rectal)</td>
<td>Facial angiofibroma, cortical tubers, renal angiomyolipoma</td>
</tr>
</tbody>
</table>
Juvenile Polyps

• Sporadic: retention polyps
• Syndromic
  – Autosomal dominant
  – 3 to as many as 100 polyps
  – Pulmonary arteriovenous malformations are a recognized extra-intestinal manifestation
• Children less than 5 years of age
• Site: rectum
• Pathogenesis: SMAD 4 (Intermediate b/w TGF beta pathway)
Peutz-Jeghers Syndrome

- Autosomal dominant syndrome
- Median age of 11 years
- Multiple GI hamartomatous polyps and mucocutaneous hyperpigmentation
- Increased risk of several malignancies, including cancers of the colon, pancreas, breast, lung, ovaries, uterus, and testicles, as well as other unusual neoplasms, such as sex cord tumors.

**Pathogenesis**

- Germline heterozygous loss-of-function mutations in the gene lkb1/stk11 (second hit)
HYPERPLASTIC POLYPS

• Common epithelial proliferations
• Sixth and seventh decades
• Lesions are without malignant potential
• Pathogenesis: decreased epithelial cell turnover and delayed shedding of surface epithelial cells
• They must be distinguished from sessile serrated adenomas
• Epithelial hyperplasia can occur as a nonspecific reaction adjacent to or overlying any mass or inflammatory lesion
NEOPLASTIC POLYPS

**Colonic adenomas**

Benign polyps that are precursors to the majority of colorectal adenocarcinomas.

**Intramucosal carcinomas**

**Carcinoid tumors**

**Stromal tumors,**

**Lymphomas,**

**Metastatic cancers**
ADENOMAS

• Adenomas are intraepithelial neoplasms that range from small, often pedunculated polyps to large sessile lesions.
• Precursors to colorectal
• West: >50 yrs (universal surveillance; 10yrs before first relative diagnosed)
TUBULAR

VILLOUS

TUBULOVILLOUS

SESSILE SERRATED

INTRAMUCOSAL CARCINOMA

CARCINOMA COLON

- M/C type: Adenocarcinoma
- Others
  - SCC
  - Neuroendocrine
  - NHL
  - Mesenchymal neoplasms
Adenocarcinoma

- Familial syndromes'
- Sporadic
<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>
</tr>
</thead>
<tbody>
<tr>
<td>Familial adenomatous polyposis (70% of FAP)</td>
<td>APC/WNT pathway</td>
<td>APC</td>
<td>Autosomal dominant</td>
<td>None</td>
<td>Tubular, villous; typical adenocarcinoma</td>
</tr>
<tr>
<td>Familial adenomatous polyposis (&lt;10% of FAP)</td>
<td>DNA mismatch repair</td>
<td>MUTYH</td>
<td>None, recessive</td>
<td>None</td>
<td>Sessile serrated adenoma; mucinous adenocarcinoma</td>
</tr>
<tr>
<td>Hereditary nonpolyposis colorectal cancer</td>
<td>DNA mismatch repair</td>
<td>MSH2, MLH1</td>
<td>Autosomal</td>
<td>Right side</td>
<td>Sessile serrated adenoma; mucinous adenocarcinoma</td>
</tr>
<tr>
<td>Sporadic colon cancer (80%)</td>
<td>APC/WNT pathway</td>
<td>APC</td>
<td>None</td>
<td>Left side</td>
<td>Tubular, villous; typical adenocarcinoma</td>
</tr>
<tr>
<td>Sporadic colon cancer (10% to 15%)</td>
<td>DNA mismatch repair</td>
<td>MSH2, MLH1</td>
<td>None</td>
<td>Right side</td>
<td>Sessile serrated adenoma; mucinous adenocarcinoma</td>
</tr>
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</table>
The diagram illustrates the progression from normal colon to carcinoma, highlighting key genetic and epigenetic alterations.

**Normal Colon**
- Mucosa
- Submucosa
- Muscularis propria

**Mucosa at Risk**
- Germ-line (inherited) or somatic (acquired) mutations of cancer suppressor genes ("first hit")
  - APC at 5q21

**Adenomas**
- Methylation abnormalities
- Inactivation of normal alleles ("second hit")
  - APC β-catenin
  - K-RAS at 12p12

**Carcinoma**
- Proto-oncogene mutations
- Homozygous loss of additional cancer suppressor genes
- Overexpression of COX-2
- Additional mutations
- Gross chromosomal alterations
  - p53 at 17p13
  - LOH at 18q21 (SMAD 2 and 4)
  - Telomerase
  - Many other genes

* Oncogene-induced senescence

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FAP

• At least *100 polyps are necessary for a diagnosis* of classic FAP, and as many as several thousand may be present.
HEREDITARY NON-POLYPOSIS COLORECTAL CANCER

• Lynch syndrome
• Familial clustering: colorectum, endometrium, stomach, ovary, ureters, brain, small bowel, hepatobiliary tract, and skin.
• Inherited mutations in genes that encode proteins responsible for the detection, excision, and repair of errors that occur during DNA replication
• Msh2 and Mlh1.
• Epigenetic silencing
• Defects in mismatch repair lead to the accumulation of mutations at rates up to 1000 times higher than normal, mostly in regions containing short repeating DNA sequences referred to as microsatellite DNA
• Resulting microsatellite instability
**NORMAL COLON**

- Mucosa
- Submucosa
- Muscularis propria

**Sequencing Events**
- Germline (inherited) or somatic (acquired) mutations of mismatch repair genes

**SESSILE SERRATED ADENOMA**

- Alteration of second allele by LOH, mutation, or promoter methylation

**CARCINOMA**

- Microsatellite instability/"mutator phenotype"
- Accumulated mutations in genes that regulate growth, differentiation, and/or apoptosis

**Gene Mutations**

- MLH1, MSH2
  - (MSH6, PMS1, PMS2)

- TGFβRII, BAX, BRAF, TCF-4, IGF2R, others

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<table>
<thead>
<tr>
<th>Revised Bethesda criteria for HNPCC screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revised Bethesda: One of the Following Criteria Need to be Met:</td>
</tr>
<tr>
<td>Diagnosed with colorectal carcinoma (CRC) before the age of 50 years</td>
</tr>
<tr>
<td>Synchronous or metachronous CRC or other Lynch syndrome (HNPCC)-related tumors (stomach, bladder, ureter, renal pelvis, biliary tract, brain (glioblastoma), sebaceous gland adenomas, keratoacanthomas, and small bowel carcinoma, regardless of age.</td>
</tr>
<tr>
<td>CRC with a high-microsatellite instability morphology (tumor infiltrating lymphocytes, Crohn-like reaction, mucinous/signet ring differentiation, or medullary growth pattern) that was diagnosed before the age of 60 years</td>
</tr>
<tr>
<td>CRC with one or more first-degree relative with CRC or other HNPCC-related tumors with one of the cancers being diagnosed under age 50 years (or adenoma under age 40 years)</td>
</tr>
<tr>
<td>CRC with two or more relatives with CRC or other HNPCC-related tumors, regardless of age</td>
</tr>
</tbody>
</table>
Adenocarcinoma

- 60 to 70 years of age
- Males
- The dietary factors: low intake of unabsorbable vegetable fiber and high intake of refined carbohydrates and fat.
- It is theorized that reduced fiber content leads to decreased stool bulk and altered composition of the intestinal microbiota.
Adenocarcinoma

- **Type**
  - Intestinal type
  - Mucinous

- **Differentiation**
  - Well
  - Moderate
  - Poorly
  - Undifferentiated

- **Other prognostic variables**
<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>Tumor invades submucosa</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades muscularis propria</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invades through muscularis propria into subserosa or nonperitonealized</td>
</tr>
<tr>
<td></td>
<td>pericolic or perirectal tissues</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor directly invades other organs or structures and/or perforates visceral</td>
</tr>
<tr>
<td></td>
<td>peritoneum</td>
</tr>
<tr>
<td></td>
<td>Regional nodal metastasis</td>
</tr>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No nodal metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in one to three pericolic or perirectal nodes</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in four to more pericolic or perirectal nodes</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in any node along course of a named vascular trunk and/or metastasis to apical node</td>
</tr>
<tr>
<td></td>
<td>Distant metastasis</td>
</tr>
<tr>
<td>MX</td>
<td>Presence of distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>
Small intestine carcinoid
Colorectal Lymphoma

• Less common in colon than small bowel or stomach
• Usually B cell lineage
• T cell patients are younger, associated with perforation and poorer prognosis
• **Risk factors**: transplants, ulcerative colitis and AIDS
• Regional lymph nodes involved in 50% of cases
• Advanced lesions may impair gut motility by destroying muscle wall
Gross description

- Plaque-like expansion of mucosa / submucosa, bowel wall thickening, polyps ("multiple lymphomatoid polyposis" if multiple polyps throughout colon) or ulceration
Tumors of the Anal Canal

- Upper zone is lined by columnar rectal epithelium
- Middle third by transitional epithelium
- Lower third by stratified squamous epithelium.
- Glandular or squamous (hpv infection, which also causes precursor lesions such as condyloma accuminatum)
- Basaloid (cloacogenic carcinoma)
Appendix

• Normal true diverticulum of the cecum
• Prone to acute and chronic inflammation.
• Lifetime risk for appendicitis is 7%; males are affected slightly more

*Pathogenesis*

• Progressive increases in intraluminal pressure that compromise venous outflow
  – Luminal obstruction
  – Fecalith
  – Gallstone,
  – Tumor,
  – Mass of worms (oxyuriasis vermicularis)
APPENDICITIS

- Peak incidence 10-12 years
- Begins as dull, steady pain in periumbilical area...
  Progresses over 4-6 hours & localizes to right lower quadrant
  - Low grade fever
  - Nausea
  - Anorexia
  - Sudden pain relief may indicate rupture of appendix (Leads to peritonitis)

*Diagnosis*

- Clinical signs and symptoms
- ↑WBC
- Abdominal Sonogram
- Exploratory Lap
- Rebound Pain or Tenderness (RLQ) at McBurney's Point
Appendix, Acute Appendicitis

red color c/w acute inflammation
Case based study GIT III
Case 1

- 56 year male presented with vague abdominal aches and pains and mild anaemia to a physician after routine lab investigations.

  – Order further evaluation
Colonoscopy
Gross
Microscopy
Microscopy
• Diagnosis
• Further work up
• Management
A definite increased risk of developing colon cancer is associated with which one or more of the following?

A. Diet high in fiber
B. Diet low in animal fat & protein
C. Ulcerative colitis
D. Familial polyposis
E. Strong family history of colon cancer in several preceding generations
Select the most common mode of spread of colon cancer

A. Hematogenous
B. Lymphatic
C. Direct extension
D. Implantation
Which of the following is the most important prognostic determinant of survival after treatment for colorectal cancer?

A. Lymph node involvement
B. Transmural extension
C. Tumor size
D. Histologic differentiation
E. DNA content
With regard to colorectal polyps, which of the following is/are considered precancerous?

A. Hyperplastic polyp
B. Juvenile polyp
C. Tubulovillous adenoma
D. Retention adenoma
A 68-year-old man presents to his primary care physician with anaemia. The patient’s medical history is significant for hypertension. The patient is found to have guaiac-positive stools and is subsequently referred for colonoscopy. Colonoscopy reveals a “golf ball”-size, near-obstructing tumor in the descending colon, not admitting the scope. The biopsy is positive for adenocarcinoma of the colon.

Q. Which of the following is the next step in the management of this patient?
A. Full metastatic workup first, and if negative, then plan for colon resection
B. A course of radiation therapy prior to any resection
C. Plan for pre-operative chemotherapy
D. Do metastatic work up, but plan for colon resection anyway
E. Schedule a barium enema to evaluate the proximal colon
Q. A 60-year-old man presents for an annual physical examination. The examination is normal except for a palpable mass in the rectum on digital rectal examination. The patient denies any change in bowel habits and feels well. Rectal cancer is suspected. What is the next best step in the evaluation of this patient?

A. Computed tomography scan of the abdomen and pelvis
B. Double-contrast barium enema
C. Flexible sigmoidoscopy with biopsy of the lesion
D. Full colonoscopy with biopsy of the lesion
E. Magnetic resonance imaging scan of the abdomen and pelvis
Q. A 70-year-old man with severe atherosclerosis who takes 1 aspirin (75 mg) daily undergoes cardiac catheterization because of chest pain. Later in the day, he develops severe abdominal pain and passes a large amount of bloody diarrhea. Physical examination reveals no peritoneal signs. Which of the following is the most likely cause of the patient’s bleeding?

A. Colon cancer  
B. Diverticulitis  
C. Hemorrhoids  
D. Mesenteric ischemia  
E. Nonsteroidal anti-inflammatory drug enteropathy
CASE 2

• 15 year old boy presented with acute pain in abdomen.

• On examination

• Pale, feeble pulse

• Low heart rate, low BP, fever.

• Abdomen is tender with no bowel sounds
• Order investigations
• CBC:
  – TLC: 25200
  – DLC: P85, L15
  – PC: 2.5

• Management