Pathology of the Lower Gastrointestinal Tract, III/III

I'M A YOUNG POLYP!!! I'VE GOT MY WHOLE NEOPLASTIC TRANSFORMATION AHEAD OF ME!!

DON'T SNARE ME!! I SWEAR I'M BENIGN!

NO ONE LIKES COLONOSCOPIES.
Learning Objectives

- Describe the clinical presentation, risk factors, pathologic findings and treatment of the small bowel carcinoid tumors

- Recognize the most common benign, premalignant and malignant colonic polyps including most common screening test for detection

- Describe the clinical presentation, risk factors, pathologic findings and treatment of the malignant colonic carcinomas
Carcinoid Tumors

- Arise from endocrine cells that release hormones coordinating intestinal functions.
- Neuroendocrine cells arise from the fetal nervous system. While most of the NE cells reside in endocrine organs, such as the thyroid and adrenal glands, a large number of them are present in, and have essential roles in the function of, the mucosa by the production and secretion of a variety of peptide hormones.
Carcinoid Tumors

Currently named well-differentiated neuroendocrine tumors.

Malignant but with indolent growth, hence the name

Most of them are asymptomatic

Most are found in the GI tract, and more than 40% occur in the small intestine

Metastases depends on location and size

- Esophagus: 1%
- Stomach and proximal duodenum: <10%
- Jejunum/Ileum: 40%
- Appendix: 25%
- Colorectal: 25%
Carcinoid Tumors: Presentation

**Carcinoid tumors without carcinoid syndrome**

No metastases

1. **Appendix, stomach, duodenum, rectum:** Discovered by chance (appendectomy, endoscopy)
2. **Jejunum/ileum:** Recurrent abdominal pain, due to obstruction

**Carcinoid tumors with systemic manifestations**

Metastases to the liver

- Majority cause *carcinoid syndrome*
- Observed in 8% of carcinoid tumors, most of which are midgut tumors
- Few may cause Cushing syndrome or acromegaly
## Carcinoid Syndrome: Manifestations

<table>
<thead>
<tr>
<th>Symptoms/Signs</th>
<th>At Presentation</th>
<th>During Course of Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>32-73%</td>
<td>68-84%</td>
</tr>
<tr>
<td>Flushing</td>
<td>23-65%</td>
<td>63-74%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>10%</td>
<td>34%</td>
</tr>
<tr>
<td>Asthma</td>
<td>4-8%</td>
<td>3-18%</td>
</tr>
<tr>
<td>Carcinoid heart</td>
<td>11%</td>
<td>14-41%</td>
</tr>
<tr>
<td>Pellagra</td>
<td>2%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Modified from: “Harrison’s Principles of Internal Medicine” 17th edition

Dermatitis of pellagra
Carcinoid Syndrome: Pathophysiologic Mechanisms

- Overproduction of serotonin, histamine, tachykinins, other hormones
- **Flushing**: Histamine and possibly tachykinins
- **Diarrhea**: Serotonin, probably tachykinins and PGE$_2$
- **Asthma**: Mediated by histamine and serotonin
- **Fibrosis** in right heart (carcinoid heart disease): Serotonin causes fibroblast proliferation by stimulating 5HT$_{2B}$ receptors on heart valves
- **Pellagra**: Inadequate tryptophan supply for synthesis of niacin
Carcinoid, gross

Yellow-tan in color that create a polypoid lesion.

In many occasions the mucosa is intact.
Carcinoid tumors, histology

Composed of islands, trabeculae, strands, glands, or sheets of uniform cells with scant, pink granular cytoplasm and round to oval stippled nucleus “salt and pepper chromatin”
Carcinoid, pathology diagnosis

CD56, Synaptophysin, Chromogranin: Positive
Carcinoid, EM

Neurosecretory granules
Carcinoid Tumors, most important prognostic factor is location

- **Foregut carcinoids:**
  - Esophagus, stomach, duodenum
  - Rarely metastasize

- **Midgut carcinoids: The bad ones**
  - Jejunum and ileum
  - **Multiple, aggressive, metastasize frequently**
  - Produce a local fibrotic reaction that may cause obstruction, by kinking or stricture

- **Hindgut carcinoids:**
  - Appendix, rectum
  - Rarely metastasize
Carcinoid Tumor Syndrome

Easy to diagnose and treat -- if you think of it.

The flushing can look like "allergy" or "rash".

The wheezing can simulate "asthma".

The diarrhea can mimic "spastic colon".

It would be better to have the correct diagnosis before the right side of the heart has inner scarring.

Even when it's metastatic in the liver, debriding the tumor can often give many good years.
Colonic Polyps

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Colonic polyps

- Inflammatory
- Hyperplastic
- Hamartomatous
- Adenomatous
- Serrated
Colonic Polyps – Inflammatory

**Inflammatory polyps:**
Secondary to chronic inflammation: IBD, solitary rectal ulcer syndrome

Composed of hyperplastic epithelium with rich inflammatory infiltrate of lamina propria

No malignant potential
Colonic Polyps – Hyperplastic

Hyperplastic polyps: Unclear pathogenesis
Occur in rectosigmoid colon, left colon
Composed of hyperplastic epithelium, goblet cells
Malignant potential …
Colonic Polyps – Hamartomatous

**Hamartoma**: Congenital malformation consisting of tissues normally present in that location but growing in a disorganized fashion

*Occur sporadically or as components of various genetically determined or acquired syndromes.*

Types of hamartomatous polyps:
- **Juvenile**
- **Peutz-Jeghers**
Colonic Polyps – Hamartomatous/Juvenile

**Solitary:** Colon and rectum, childhood (younger than 5 years), no malignant potential, usually <3cm

**Juvenile polyposis syndrome:**
- Hereditary, autosomal dominant (mutation of SMAD4)
- > 5 juvenile polyps in the colon/rectum or multiple throughout the GI tract.
- Increased risk of adenocarcinoma

**Presentation:** Bleeding, pain, diarrhea, microcytic anemia
Colonic Polyps – Hamartomatous Peutz-Jeghers syndrome

- **Autosomal dominant**, mutation of STK11 tumor suppressor gene
- Combination of hamartomatous polyps and mucocutaneous pigmentation.

[Image of colon with polyps]

http://www.genetics4medics.com/peutz-jeghers-syndrome.html
**Pigmented macules:** perioral, perianal, periorbital, hands, feet and genitalia

**Hamartomatous polyps** in small intestine, colon and other sites

**Intussusception of small bowel**

Markedly **increased risk of several malignancies:** GI tract, pancreas, cervix, breast, ovary (By age 60, almost all patients have developed some malignancy)
**Colonic Polyps – Hamartomatous Peutz-Jeghers syndrome**

**Hamartomatous polyp in Peutz-Jeghers syndrome**: Arborizing network of connective tissue, smooth muscle, lamina propria, and glands lined by normal-appearing intestinal epithelium. The arborization and presence of smooth muscle intermixed with lamina propria are helpful in distinguishing polyps of PJS from juvenile polyps.
Colonic Polyps – Adenomatous

- Benign glandular **neoplasms**
- **Precursors of majority of colorectal adenocarcinoma**
- Because of risk of malignancy, screening colonoscopy should start screening at 50.
- Present in 30% of all people >60 year old
- Pedunculated or sessile
- **Dysplasia** is present
- Usually clinically silent
Colonic Polyps – Adenomatous

- **Malignant transformation** related to:
  - **SIZE**  Most important
  - **Dysplasia**
  - **Architecture:** tubular, tubulo-villous, villous

- **Prevention** of colorectal cancer (CRC): Screening by colonoscopy beginning at age 50
Adenomatous polyps

Dysplasia: Cell crowding, stratification, loss of orderly maturation from crypt to surface, nuclear hyperchromasia.
Familial Adenomatous Polyposis (FAP):

- Autosomal dominant
- Mutations of Adenomatous Polyposis Coli gene – \textit{APC} gene (tumor suppressor)
- Innumerable colorectal adenomatous polyps, which will eventually become cancer
- Mean age of CRC in untreated patients: 39 years
- Accounts for 1% of CRC
- Only prevention: \textit{Colectomy}

\textbf{FAP:} The colonic mucosa is carpeted with innumerable polyps
Familial Syndromes: Variants of FAP

- **Gardner Syndrome:**
  - FAP + Supernumerary teeth, osteomas, desmoid tumors, retinal hyperplasia

- **Turcot Syndrome:**
  - FAP + Glioblastoma
  - Lynch syndrome + Medulloblastoma
Familial Syndromes: Hereditary Nonpolyposis Colorectal Cancer (Lynch Syndrome)

- Autosomal dominant
- Accounts for 5% of all colon cancers
- Mutations of DNA mismatch repair (MMR) genes leading to microsatellite instability (MSI): MLH1, MSH2, MSH6, PMS2
- Lifetime risk of CRC: 80%
- CRC usually in the right colon
- Mean age at presentation: 47 years
- No polyps
- Other cancers: Endometrium, ovaries, stomach, urinary tract, small bowel, biliary tract, brain, etc.
Colorectal Cancer (CRC)

- **Third** most frequent cause of cancer-related deaths
- Incidence peaks at **60-70** years of age
- **Adenocarcinoma** arising from stem cells of crypts
CRC: Morphology

- 65% distal, 35% proximal to splenic flexure
- Exophytic mass in right colon, infiltrative in the left colon

Apple-core sign, AKA napkin ring signs
CRC is an adenocarcinoma

Hepatic metastases of a CRC
CRC: Etiology/Risk Factors

- **Associated with familial syndromes:** 5% of cases
  - Lynch syndrome (HNPCC): Risk 70-80%
  - FAP and variants: Risk close to 100%
  - Hamartomatous polyposis syndromes: Peutz-Jeghers and juvenile polyposis

- **Familial:** 25% of cases
  - Risk in the general population: 6%
  - Risk in people with history of CRC in first-degree relatives: 15-20%

- **Sporadic:** 70% of cases No family history
  - **Polyps:** Adenomatous and serrated
  - IBD
  - Aging
  - Diet: High-fat, low-fiber, rich in red meat
  - Alcohol and smoking
Molecular pathogenesis of Colorectal carcinoma

Two molecular pathways described:

1. Microsatellite instability pathway (15%)
   Alternate/Serrated Pathway

2. APC/betha-catenin (chromosomal instability) pathway (85%)
CRC: Pathogenesis – Alternate/Serrated Pathway

**Alternate pathway**

Morphologic correlate: **Sessile serrated polyp** (right colon)

Early event: Mutations of **DNA mismatch repair genes**, leading to **microsatellite instability**

Mutations in **BRAF** or **K-RAS**
Adenoma-Carcinoma sequence

**Morphologic correlate:** Adenomatous polyp

**Early event:** Mutations of APC gene

APC protein participates in degradation of β-catenin
Without functional APC, β-catenin translocates into nucleus and activates growth-promoting genes
CRC: Presentation

Common symptoms:
- Hematochezia
- Anemia, manifesting with fatigue, dizziness, palpitations
- Abdominal pain
- Altered bowel habits
- Weight loss

Right-sided tumors:
- Occult bleeding, anemia

Left-sided tumors:
- Changes in bowel habits (constipation, diarrhea)
- Hematochezia

Advanced cancer: Cachexia
CRC: Prognosis

*Stage* is the best predictor of survival
CRC: Survival

![Bar chart showing survival rates for different stages of CRC (Carcinoma of the Rectum and Colon).]
The End