

TUMORS OF THE SMALL INTESTINE, LARGE INTESTINE, AND APPENDIX

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OBJECTIVES:

- Know the histology of non-neoplastic polyps and how they differ from neoplastic polyps
 - Understand the types of hereditary colon cancer syndromes and their risk of colon cancer
 - Understand the adenoma-carcinoma sequence
 - Know the non-carcinomatous lesions of the small and large bowel
 - Understand the pathogenesis and pathology of acute appendicitis
- I. **Polyp:** A grape-like protrusion of tissue into the bowel lumen.
- a. **Sessile:** flat on the mucosal surface
 - b. **Pedunculated:** Has a stalk
 - c. **Epithelial or submucosal**
 - d. **Non-Neoplastic Polyps:**
 - i. **Hyperplastic polyps:**
 1. Most common polypoid lesion of the colon
 2. Sessile with a rounded surface.
 3. Histologically: well differentiated glandular epithelial cells arranged in a "saw-toothed" pattern
 4. Majority have no malignant potential.
 - a. Some right sided polyps may be precursors of colorectal cancer.
 - ii. **Juvenile Polyps** (retention polyps) (Syndrome):
 1. Small rounded pedunculated polyps
 - a. Usually found in the rectum.
 2. Hamartomatous proliferations
 - a. Dilated cystic glands
 3. Children under 10 years of age are usually affected,
 - a. May also occur in adults.
 4. There is a strong tendency for these polyps to bleed
 5. No cancer potential
 6. Rare autosomal dominant juvenile polyposis syndrome
 - a. Multiple juvenile polyps throughout gi tract.
 - b. Increased risk carcinoma
 - iii. **Peutz-Jegher Polyps** (Syndrome):
 1. Autosomal-dominant trait
 - a. Germline mutation in LKB1 gene (serine threonine kinase)
 2. Hamartomatous epithelial polyps in the gastrointestinal tract
 - a. Mostly in small bowel
 3. Mucocutaneous melanin pigmentation.
 4. No malignant potential, however these patients are at

5. increased risk of carcinoma of pancreas, breast, lung, ovary and uterus.

iv. Cowden Syndrome

1. Hamartomatous epithelial and non-epithelial polyps
2. Mutation in PTEN (phosphatase and tensin homologue) tumor suppressor gene
 - a. Increased risk of tumors in thyroid, breast, uterus, and skin.

e. Adenomatous Polyp (neoplastic):

- i. Epithelial proliferations with dysplasia
 1. Thought to give rise to most colon cancers
- ii. Classified base on architecture
 1. **Tubular Adenomas: 90%**
 - a. Stalked polyp with a rounded surface very much like a mushroom
 - b. Two-thirds of adenomas (not polyps) in the colon.
 - c. Usually small, less than 2 cm
 - d. 50% are located in the rectosigmoid colon.
 - e. Histology:
 - i. Epithelial tubules
 - ii. Dysplasia
 1. Mild dysplasia to frank carcinoma. .
 2. **Villous Adenoma: 1%**
 - a. Typically large (2 cm. to 15 cm.)
 - b. Broad-based sessile lesion with a gross appearance similar to a cauliflower
 - c. Histology: Finger-like projections of epithelial cells supported by a fibrovascular core.
 3. **Tubulovillous Adenoma: 5-10%**
 - a. Mixture of tubular and villous architecture
- iii. Malignant potential is based on their **size**:
 1. 1 cm. or less polyp has a very small chance of harboring a carcinoma
 2. Polyp greater than 4 cm. has a 40% chance

II. Inherited Syndromes:

- a. **Familial Polyposis Syndromes:** The following syndromes all are autosomal-dominant and have a germline abnormal APC (Adenomatous Polyposis Coli) gene on chromosome 5 (5q21). All are characterized by multiple, greater than 100, colon adenomas. The average age of onset of polyps is second to third decade, followed by cancer within 10 -15 years unless surgical resections interrupt the natural history.
 - i. Familial Polyposis Coli
 - ii. **Gardner's Syndrome:** Characterized by polyps not only in the colon, but also in the stomach and the small intestine around the ampulla of Vater; plus, osteomas of the skull, mandible, and long bones and soft tissue tumors of the skin.
 - iii. **Turcot's Syndrome:** A rare entity, which is essentially familial polyposis coli plus malignant central nervous system tumors.

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- b. Hereditary Nonpolyposis Colorectal Cancer (HNPCC, or Lynch Syndrome)**
 - i. Autosomal dominant
 - ii. Increased risk of colorectal cancer and extraintestinal cancers
 - iii. Malignancies proximal to splenic flexure
 - 1. Cancers occur 40 to 50 years old
 - iv. Defect of **DNA repair genes**
 - III. Colorectal Carcinoma**
 - i. 98% of all cancers in the large intestine are adenocarcinomas
 - a. Epidemiology**
 - i. Risk Factors:
 - 1. Diet:
 - a. Low fiber diet
 - b. High content of refined carbohydrates
 - c. Increased intake of fat
 - d. Decreased protective micronutrients (vit A, C, E)
 - 2. Age: Getting old increases risk of developing cancer
 - a. Peak incidence in 70's
 - 3. Pre-existing Conditions:
 - a. Villous adenomas
 - b. Tubular adenomas (slight)
 - c. Ulcerative colitis
 - d. Crohn's colitis
 - e. Inherited syndromes
 - f. Previous colon carcinoma
 - 4. Protective effect of aspirin and other NSAIDs
 - a. Cyclooxygenase-2 (cox-2) enzyme inhibition
 - ii. **Adenoma-Carcinoma Sequence** (Molecular Biology of Colon Cancer)
 - i. Adenoma is the precursor lesion for carcinoma
 - 1. Populations with increased adenomas have increased carcinoma
 - 2. Distribution of adenomas and carcinoma is similar
 - 3. Peak incidence of adenomas antedates peak for carcinoma
 - 4. Early invasive cancers have adenomas at the edge
 - 5. Risk of cancer related to number of adenomas
 - 6. Screening and removing polyps decreases cancer incidence
 - ii. Cumulative alterations in the genome lead to progressive increase in size, level of dysplasia, and invasive potential of neoplastic lesions.
 - iii. Two pathways
 - 1. APC/B-catenin pathways (Vogelgram- Multihit hypothesis)
80% of sporadic carcinoma, morphologic counterparts
 - a. Loss of APC tumor suppressor gene
 - i. Cell adhesion
 - ii. Accumulated B-catenin translocates to the nucleus and activates transcription of several genes.

- b. K-RAS oncogene activated by mutation
 - i. Intracellular signal transduction
 - ii. Trapped in activated state that delivers mitotic signals and prevents apoptosis
- c. 18q21 loss
 - i. DCC gene (Cell adhesion molecule)
 - ii. DPC4/SMAD4, and SMAD 2 genes (components of transforming growth factor B signaling pathway)
- d. Loss of TP53 (17p)
 - i. Tumor suppressor gene (molecular policeman)
- 2. MSI pathway (DNA mismatch repair genes), no clear morphologic correlate
 - a. Mutation in DNA mismatch repair gene
 - i. 5 genes (MSH 2, MSH6, MLH1, PMS1, PMS2)
 - 1. MLH1 most common in sporadic
 - ii. Hypermutable state
 - 1. Microsatellite instability (MSI)
 - a. Simple repetitive DNA sequences (non-coding) are unstable during DNA replication
 - b. Mutation of other genes
 - i. Type II TGF- β receptor (cell growth when mutated)
 - ii. BAX (prevent apoptosis when mutated)
 - c. ? if some hyperplastic polyps are precursor lesion
 - d. Tumors have distinctive morphological features
 - i. Proximal colonic location
 - ii. Mucinous histology
 - iii. Infiltration by lymphocytes
 - iv. Better prognosis (stage for stage compare to APC/B-catenin pathway tumors)

c. Pathology

- i. Site
 - 1. 25% caecum or ascending, 25% transverse, 25% descending and sigmoid, 25% rectal and distal colon.
- ii. Gross
 - 1. Left colon (Distal): Gross lesions begin as flat plaques that have a strong tendency to grow into annular "napkin ring" lesions. Central ulceration and penetration of tumor into bowel wall is common.
 - a. Obstruction common.
 - 2. Right colon (Proximal): These cancers tend to grow as exophytic, polypoid masses.
 - a. Obstruction uncommon
- iii. Histology:
 - 1. Adenocarcinomas (gland forming)
 - a. Mucin-producing malignant cells forming glands in varying degrees of disorganization
 - i. Increased mucin, poorer prognosis

iv. Staging: TNM System

Stage	Description	5 year survival
Tumor (T)		
0	No tumor	100
Is	In situ (limited to mucosa)	100
1	Invasion of submucosa	97
2	Invasion of muscularis propria	90
3	Invasion of subserosa	78
4	Invasion of contiguous structures	63
Lymph Nodes (N)		
0	No lymph node metastasis	
1	1 to 3 pericolic nodes	66
2	4 or more pericolic nodes	37
3	Node along named blood vessel	
Distant Metastasis (M)		
0	No distant metastasis	
1	Any distant metastasis	4

d. Clinical features

- i. Left sided lesions
 1. Occult bleeding, changes in bowel habits, crampy left lower quadrant discomfort
- ii. Right sided lesions
 1. fatigue, weakness, iron deficiency anemia
 - a. iron deficiency anemia in an older man means gi cancer until proven otherwise
- iii. Detection
 1. Digital rectal exam and fecal occult blood test
 2. BE, endoscopy
 3. CT assess metastatic spread

- IV. **Small Intestine:** Tumors of the small intestine are relatively rare.
- a. **Benign Tumors:**
 - i. Stromal Tumors
 - ii. Adenomas
 - iii. Lipomas
 - b. **Malignant Tumors:**
 - i. **Adenocarcinoma**
 1. 50% of total malignant tumors specifically located in the small intestine.
 - a. Usually found in the duodenum or jejunum
 2. Grow in an annular configuration
 3. Similar histology to colon.
 - ii. **Carcinoid:**
 1. Endocrine
 - a. Part of the amine precursor and decarboxylation (APUD) system.
 - i. Generate bioactive compounds
 1. Peptide and nonpeptide hormones
 2. All are considered malignant
 - a. Risk factors for aggressiveness
 - i. Site of origin
 1. Appendiceal and rectal rarely metastasize
 - ii. Depth of penetration
 1. Halfway through muscle more likely malignant
 - iii. Size
 1. Greater than 2
 3. Pathology:
 - a. Site
 - i. Appendix > small bowel > rectum > stomach > colon
 - b. Gross
 - i. Yellow submucosal nodules
 1. Annular, polypoid or intramural
 - c. Microscopically
 - i. Monotonous round cells
 1. Nests, cords, and/or rosettes.
 2. Eosinophilic cytoplasm
 - a. Neurosecretory granules
 - ii. Stain with chromogranin A, synaptophysin.
 4. Clinical Features:
 - a. Secretory products
 - i. Carcinoid Syndrome
 1. Diarrhea, flushing, bronchospasm, cyanosis, telangiectasis and skin lesions.
 2. Serotonin elaboration

- ii. Zollinger-Ellison syndrome
 - 1. Gastrin
 - 2. Peptic ulcers
 - iii. Cushing's syndrome
 - 1. ACTH secretion
 - b. 5 year survival 90%
- V. **Lymphomas:**
 - a. **Secondary**
 - i. Dissemination of systemic lymphoma
 - b. **Primary**
 - i. Western type:
 - 1. **MALT** (Mucosal associated lymphoid tissue) Lymphomas
 - a. B-cell lymphoma
 - b. Stomach most common site
 - c. Associated with Helicobacter pylori
 - d. Histology
 - i. Diffuse lymphoid proliferation, intermediate sized cells
 - ii. **Lymphoepithelial** lesions
 - 1. Destruction of epithelium by malignant lymphocytes
- VI. **Appendix:**
 - a. **Appendicitis**
 - i. Most common acute abdominal condition surgically treated
 - 1. 10% of population
 - 2. Peak 2nd to 3rd decades
 - ii. Pathogenesis
 - 1. Obstruction
 - a. Fecalith
 - b. Gallstone
 - c. Tumor
 - d. Ball of worms
 - 2. Ischemic Injury
 - iii. Histology
 - 1. Neutrophils in the muscularis propria
 - 2. Three types
 - a. Early acute appendicitis
 - b. Acute suppurative appendicitis
 - c. Acute gangrenous appendicitis
 - iv. Clinical features
 - 1. Classic case
 - a. Mild periumbilical discomfort
 - i. Then right lower quadrant tenderness
 - b. Anorexia, nausea and vomiting
 - c. Fever and leukocytosis

2. Differential diagnosis

- a. Mesenteric lymphadenitis
- b. Gastroenteritis
- c. Pelvic inflammatory disease
- d. Ectopic pregnancy
- e. Meckel's diverticulitis

b. Tumors

- i. Carcinoid: most common
- ii. Mucocele
 - 1. Dilatation of lumen by mucinous secretion.
- iii. Mucinous neoplasms
 - 1. Mucinous cystadenoma
 - 2. Mucinous cystadenocarcinomas
 - a. Pseudomyxoma peritonei

REVIEW QUESTIONS:

_____ 1. Which of the following polyp is implicated in the APC/B-catenin pathway?

- A. Tubular adenoma
- B. Hyperplastic polyp
- C. Juvenile polyp
- D. Inflammatory polyp

_____ 2. Which of the following syndromes is not associated with a mutation of the APC gene and not associated with an increased risk of colon cancer?

- A. Familial Polyposis Coli
- B. Gardner's syndrome
- C. Turcot's syndrome
- D. Peutz-Jegher syndrome
- E. None of the above

_____ 3. The most common cancer of the colon is?

- A. Adenocarcinoma
- B. Squamous cell carcinoma
- C. Lymphoma
- D. Sarcoma
- E. Carcinoid tumor

_____ 4. The most common cancer of the small intestine is?

- A. Adenocarcinoma
- B. Squamous cell carcinoma
- C. Lymphoma
- D. Sarcoma
- E. Carcinoid tumor

_____ 5. Risk factors for colorectal cancer includes all of the following except?

- A. Low fiber diet
- B. Low fat diet
- C. Old age
- D. Villous adenomas
- E. Ulcerative colitis

_____ 6. Tumors of which area do not typically present with obstruction?

- A. Small bowel
- B. Left colon
- C. Right colon
- D. All of the above
- E. None of the above

_____ 7. Most common tumor of the appendix is?

- A. Adenocarcinoma
- B. Squamous cell carcinoma
- C. Lymphoma
- D. Sarcoma
- E. Carcinoid tumor

ANSWERS:

- 1. A
- 2. D
- 3. A
- 4. A
- 5. B
- 6. C
- 7. E