Case scenario

Colonic Polyps And Tumors

objectives

- Colon cancer and its epidemiology.
- Compare the pathology and clinical features of right-sided colonic adenocarcinoma and left-sided colorectal adenocarcinoma.
- Describe the relationship between prognosis and the various stages of cancer of the colon and rectum as noted in the TNM classification and staging system.
- Describe the relationship between CEA and recurrence following resection of the primary tumor.
- Mention the significant of carcinoid tumor and its features.
- Know the classification of intestinal tumors.
- Know the definition of a polyp.
- Compare adenomatous/neoplastic polyps and non neoplastic polyps with respect to pathology.
- Know the three subtypes of adenomatous polyps.
- Describe the adenomatous polyp-cancer sequence and the features associated with risk of malignancy.
- Describe the classification of the hereditary syndromes involving the GI tract and the syndromes associated with an increased risk of cancer.

Black: original content
Red: Important
Green: only found in males slides

Orange: Doctor notes
Grey: Extra/Robbins
Purple: Only found in females slides

Reviewed by: Razan AlRabah & Ibrahim AlDakhil

Editing File

Tumors of intestine

Polyps

Non-neoplastic 90%

- Hyperplastic
- Hamartomatous
- Inflammatory
- lymphoid

Neoplastic 10%

- Adenomas

Tumors

Large intestine

- Adenocarcinoma

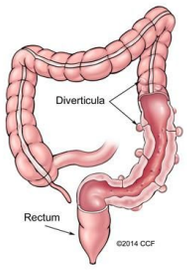
Small intestine

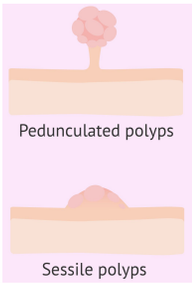
- Carcinoid
- adenocarcinoma
- Lymphoma
- leimyosarcoma

Benign tumors of intestine

Polyps

- Abnormal growth of tissue, protruding from a mucous membrane, usually benign but some can develop into cancer.
  - **Pedunculated polyp:** attached to the surface by a stalk.
  - **Sessile polyp:** attached directly without a stalk.
- **Diverticula:** Small bulging of the colonic mucosa and submucosa through weaknesses of muscle layers in the colon wall.

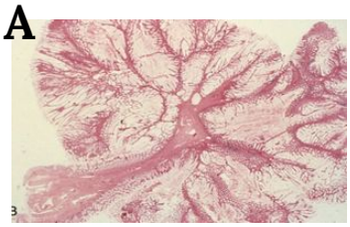


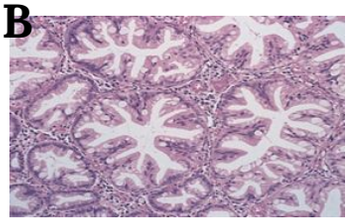


Non-neoplastic polyps (90%)

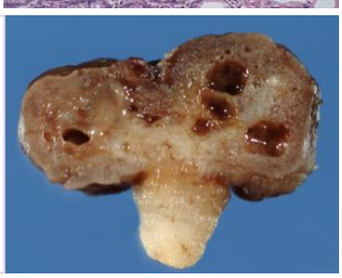
1- Hyperplastic polyps

- Asymptomatic.
- More than 50% are located in the **rectosigmoid.**
- **Most common type in adults.**
- **A:** Sawtooth surface.
- **B:** Star shaped crypts.
- Composed of well-formed glands and crypts lined by differentiated goblet or absorptive cells.
- No malignant potential or polyposis syndromes.





Smooth eroded surface with numerous mucus retention cysts, typical of sporadic juvenile polyps.



2- Hamartomatous polyps[1]

A. Juvenile Polyps (retention polyp):

- **Developmental malformations** affecting the glands and lamina propria
- Commonly occur in **children under 5 years** old in the rectum.
- In adult called retention polyp
- No malignant potential.

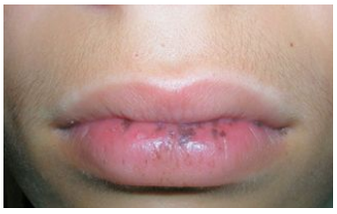
Female's slides

Juvenile polyposis		
Hereditary		Non-hereditary
Autosomal dominant	**Cowden syndrome**	**Cronkhite-Canada syndrome**
• **TGF-β** signaling pathway abnormalities. • Juvenile polyps; risk of gastric, small intestinal, colonic, and pancreatic adenocarcinoma.	• Abnormality in **PTEN** • Hamartomatous polyps, lipomas, ganglioneuromas, inflammatory polyps; increased risk for colon cancer and cancer of thyroid and breast.	• Polyps plus **ectodermal abnormalities** (Nail atrophy, hair loss, abnormal skin pigmentation) cachexia, and anemia.

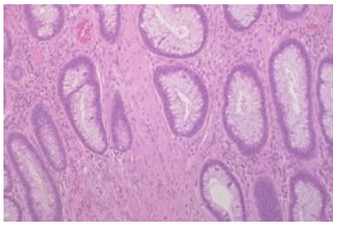
1- Tumor of tissue embryologically related to its origin (as opposed to teratoma).

Polyps Cont.

B. Peutz-Jehgers syndrome:

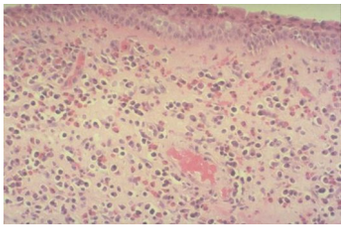


- Rare, autosomal dominant.
- Hamartomatous polyps.
- Mucosal & cutaneous pigmentation around the lips, oral mucosa, face and genitalia.
- Present with red blood in stool.
- Polyps tend to be **large** and **pedunculated**.



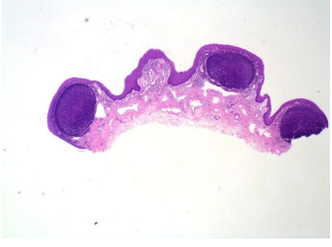
- Increased risk of developing carcinoma of the pancreas, breast, lung, ovary and uterus.
- Present at 10-15 years of age.
- Mutated gene: LKB1/STK11 which encodes a tumor suppressive protein kinase that regulates cellular metabolism.

3. Inflammatory Polyps



- Longstanding IBD, especially in chronic **ulcerative colitis.**
- Represent an exuberant reparative response to longstanding mucosal injury called pseudopolyps.

4. Lymphoid Polyps



- Reactive peyer's patch
- Mucosa is normal

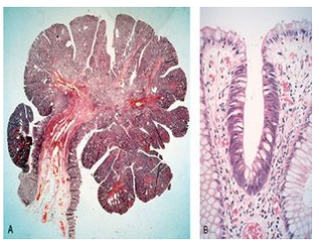
Neoplastic Polyps

Adenomatous Polyp (adenoma)

- Occur mainly in **large bowel.**
- Sporadic and familial.
- Vary from small pedunculated to large sessile.
- Epithelium proliferation and **dysplasia.**

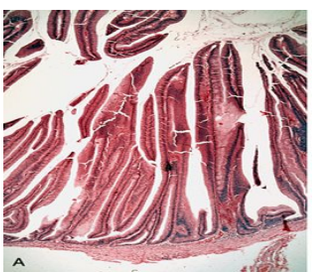
Divided into:

1. Tubular adenoma (less than 25% villous structures)

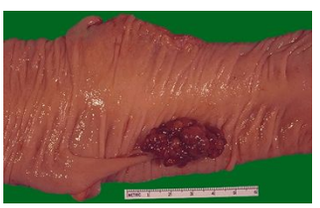


- Most common.
- 75 % occur in the distal colon and rectum.
- **Sigmoid colon** most common site.

2. Villous adenoma (villous structures more than 50%)



- The least common.
- Largest and most likely **to become malignant.**
- Age: 60 to 65 years, 75% located in **rectosigmoid** area.
- Symptoms:
  - **Rectal bleeding** or anemia.
  - Large ones may secrete mucoid material rich in **protein** and **K^+**
    - Therefor causes **hypoalbuminemia** & **hypokalemia.**



3. Tubulovillous adenoma (Villous architecture between 25 and 50%)

- 20%–30% of polyps
- Intermediate in size, degree of dysplasia and malignant potential between tubular and villous adenomas.

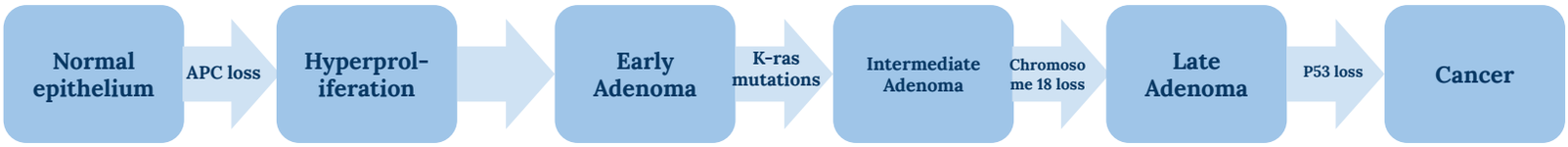
Relationship of Neoplastic Polyps to Carcinoma

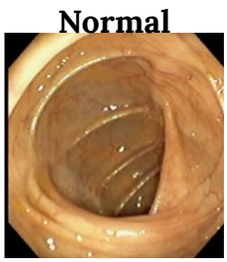
- The probability of carcinoma occurring in a neoplastic polyp is related to:
  1. The **size** of polyp.
  2. The relative proportion of its **villous features.**
  3. The presence of significant cytologic atypia (dysplasia) in the neoplastic cells.
  4. Multiple polyps.

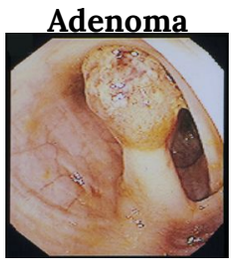
Neoplastic polyps and Carcinoma

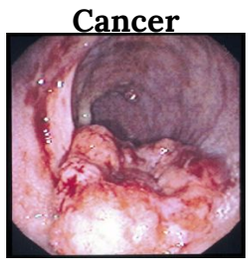
Adenoma to Carcinoma pathway

- Adenoma to carcinoma sequence is documented by several genetic alterations.




Normal


Adenoma

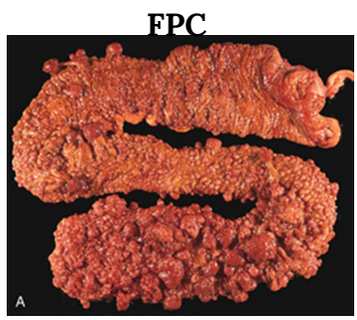

Cancer

Familial Polyposis syndromes

- Patients have genetic tendencies to develop neoplastic polyps.

Familial polyposis coli (FPC):

- Genetic defect of Adenomatous polyposis coli (APC).
- APC gene is a tumor suppressor gene located on the long arm of chromosome 5 (5q21).
- Innumerable neoplastic polyps in the colon (500 to 2500)
- Polyps are also found elsewhere in alimentary tract
- The risk of colorectal cancer is 100% by midlife.


FPC

Gardener's syndrome:

- Polyposis coli; Present at 10-15 years of age.
- Multiple Osteomas
- Epidermal cysts
- Fibromatosis

Turcot syndrome:

- Polyposis coli; Present at 10-15 years of age.
- Glioma (look for brain symptoms)
- Fibromatosis
- CNS tumors; medulloblastoma.

Malignant tumors of intestine

Introduction

- Tumors of the small and large intestines:
  1. Carcinoma.
  2. Carcinoid tumor.
  3. Lymphoma.
- The small intestine is an uncommon site for benign and malignant tumors.

Adenocarcinoma

- Adenocarcinoma of the colon is the **most common** GI malignancy

Epidemiology

- Major cause of morbidity and mortality worldwide.
- Constitutes 98% of all cancers in the large intestine.
- Incidence peaks at 60 to 70 years of age.
- Aspirin or other NSAIDs have a protective effect.

Predisposing factors

- IBD, adenomas, polyposis syndrome.
- **Diet** appears to play an important role in the risk for colon cancer:
  - Low fibre diet.
  - High fat content.
  - Alcohol
  - Reduced intake of vit A, C & E (antioxidants)

Why does less fibers and more fat intake predispose?

- Large stool bulks usually wipe off toxic oxidative byproducts produced by normal flora.
- Smaller stool bulks allows the toxic byproducts to stay on the mucosa for longer time.
- Since reduced fiber intake causes a decrease in stool size, the byproducts increased time on the mucosa will lead to oxidative damage.
- High fat intake increases production of bile acids and cholesterol.
- Which can be converted by normal flora to carcinogens.

Malignant tumors of intestine

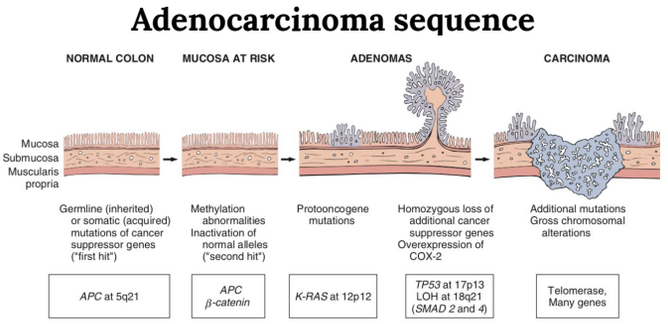
Adenocarcinoma of Large Intestine

Carcinogenesis

- Two pathogenetically distinct pathways for the development of colon cancer, both seem to result from accumulation of multiple mutations:

1- The APC/B-catenin pathway (85%):

- Chromosomal instability that results in **stepwise accumulation** of mutations in a series of oncogenes and tumor suppressor genes.



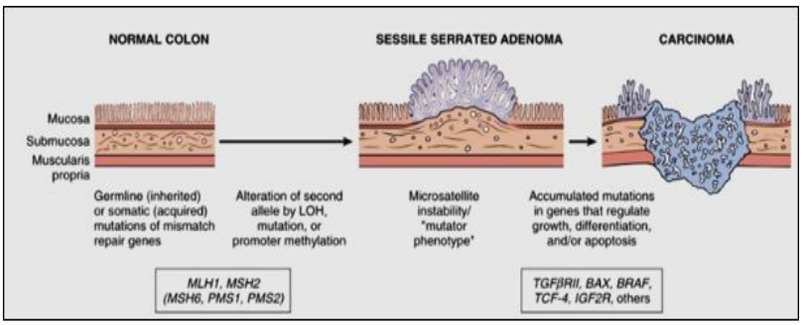
- Hereditary mutation of the APC gene is the cause of **familial adenomatous polyposis (FAP)**, where affected individuals carry an almost 100% risk of developing colon cancer by age 40 years.

2- The DNA mismatch repair genes pathway:

- Referred to as MSI high, or MSI-H tumors.
- 10% to 15% of sporadic cases.
- There is accumulation of mutations
- Five DNA mismatch repair genes **(MSH2, MSH6, MLH1,** PMS1**, & PMS2)**
- Give rise to the **hereditary non polyposis colon carcinoma (HNPCC) syndrome:**

Females slides

  - This result in microsatellite instability and permit accumulation of mutations in numerous genes.
  - If these mutations affect genes involved in cell survival and proliferation, cancer may develop.
  - It progress from normal to sessile serrated adenomas to adenocarcinoma.
  - May produce abundant mucin that accumulates within the intestinal wall, and these carry a poor prognosis.

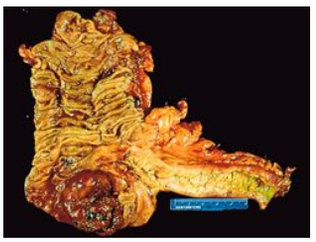


Malignant tumors of intestine

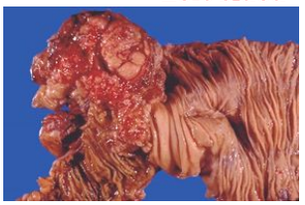
Colorectal Carcinoma

Gross pathology

Right sided



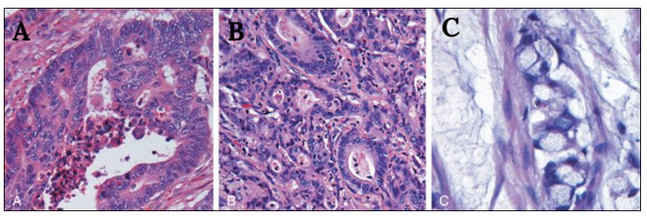
Left sided



- 70% are in the rectum, rectosigmoid and sigmoid colon.
- **Left-sided carcinomas** tend to be
  - Annular, encircling lesions
  - Early symptoms of obstruction. (bleeding in stool)
- **Right-sided carcinomas**
  - Grow as polypoid,fungating masses
  - Obstruction is uncommon.
  - Chronic bleeding leads to Anemia, and hard to detect

Microscopy

A,B: Adenocarcinoma: consist of infiltrating glands lined by atypical cells.
C: Mucinous adenocarcinoma secret abundant mucin that may dissect through cleavage planes in the wall.



Signs and symptoms

- **Rectal bleeding (PR):** If located closer to the anus.
- Change in bowel habit, feeling of incomplete defecation.
- **Bowel obstruction:** A tumor that is large enough to fill the entire lumen of the bowel.
- Right-sided lesions are more likely to bleed while left-sided tumors are usually detected later and could present with bowel obstruction.

Tumor markers & prognosis

- A substance found in the blood, urine or body tissues that can be elevated in cancer, among other tissue types.
- Tumor markers that are useful to **asses recurrence:**
  - **Carcinoembryonic antigen (CEA):** may also be raised in some non-neoplastic conditions like ulcerative colitis, pancreatitis, cirrhosis, COPD, Crohn's disease as well as in smokers.
  - **Carbohydrate antigen (CA19-9):** raised in patients with colon cancer and pancreatic cancer, esophageal cancer and hepatocellular carcinoma, elevated levels may also occur in pancreatitis and cirrhosis.
- **Tissue inhibitor of metalloproteinases 1 (TIMP1):** early as well as late stage diseases.
- The most important prognostic factors: depth of invasion, the presence or absence of lymph node metastases and distant metastasis.
- Tumor Node Metastasis (TNM) and Duke classification used for Staging of Colon Cancers.

Malignant Small intestinal Neoplasms

Malignant Small intestinal Neoplasms

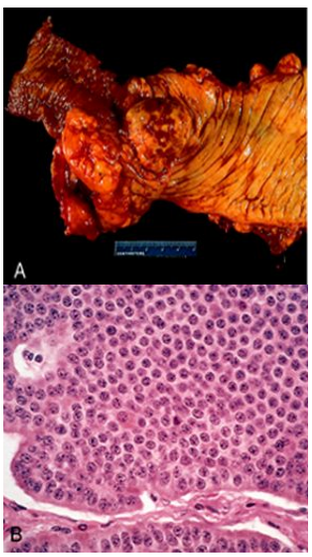
1. Carcinoid (most common)
2. Adenocarcinomas
3. Lymphomas
4. Leiomyosarcomas. (least common)

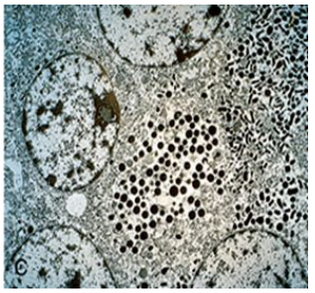
Carcinoid Tumors

- Neoplasms arising from **endocrine cells** found in the GI mucosa.
- The peak incidence: sixth decade, but they may appear at any age.
- They compose less than 2% of colorectal malignancies
- Almost half of small intestinal malignant tumors: 60 to 80% appendix and terminal ileum
- 10 to 20% rectum.

Behavior: aggressive behavior correlates with: **(Females slides)**

1. **Site of origin:**
   - **Appendiceal** and rectal carcinoids rarely metastasize, even though they may show extensive local spread.
   - 90% of **ileal, gastric,** and **colonic** carcinoids that have penetrated halfway through the muscle wall have **spread to lymph nodes** and distant sites at the time of diagnosis, especially those larger than 2 cm in diameter.
2. **Depth of local penetration**
3. **Size of the tumor**





Morphology

A: A solid, yellow-tan appearance.
B: The cells are monotonously similar, having a scant, pink granular cytoplasm and a round to oval stippled nucleus.
C: Ultrastructural features: neurosecretory electron dense bodies in the cytoplasm.

Clinical features

- Asymptomatic
- May cause obstruction, intussusception[1] or bleeding.
- May elaborate hormones: Zollinger-Ellison, Cushing's carcinoid or other syndromes.

1- Segment of small bowel will be drawn into next segment of the bowl

Malignant Small intestinal Neoplasms

Carcinoid Syndrome (Caused by Carcinoid tumor)

- 1% of carcinoid tumor & in 20% of those of widespread metastasis.
- The **principal chemical mediator** is **serotonin** and other bioactive compounds (e.g., histamine, bradykinin).
- The syndrome is classically associated with ileal carcinoids with **hepatic metastases.**

Clinical findings

- Paroxysmal flushing due to **vasodilation**[1] and serotonin.
- Episodes of asthma-like wheezing due to bronchospasm.
- Attacks of watery diarrhea & abdominal pain.
- Facial telangiectasia
- Tricuspid regurgitation and pulmonary stenosis due to increases collagen production in the valves caused by serotonin → Right-sided heart failure.

Serotonin and diarrhea (Females slides)

- Diarrhea in carcinoid patients has two components
  - **Secretory component**: due to increased serotonergic stimulation of submucosal secretomotor neurons.
  - **Motor component:** faster small bowel and colon motility as a exaggerated response to ingestion of food

Lymphoma

- Most often **low-grade** lymphomas arising in mucosal-associated lymphoid tissue (**MALT**) lymphoma
- **high-grade non-Hodgkin's** lymphomas of B cell type, May occur in any part of the intestine;
- The **ileocecal** region is a favored site for **Burkitt's lymphoma**.

1- May be triggered by emotion, alcohol, other food.

Summary

Benign tumors of the intestine

Polyps

- **Non-neoplastic polyps (90):** no dysplasia
  1. **Hyperplastic polyps:** sawtooth surface, star-shaped crypts.
  2. **Hamartomatous polyps (A: Juvenile & B: Peutz-Jeghers polyps):**
     A: occur in children under 5 y.o in the rectum.
     B: rare, autosomal dominant, increased risk of developing carcinoma.
  3. **Inflammatory polyps:** pseudopolyps caused by IBD or chronic UC.
  4. **Lymphoid polyps**
- **Neoplastic Polyps (10%):** there is dysplasia

Adenoma: occurs mainly in large bowel, sporadic and familial, epithelium proliferation and Dysplasia, divided into:

1. Tubular adenoma. 2. Villous adenoma. 3. Tubulovillous adenoma.

- **Syndormes related to polyps:**
- **1. Familial polyposis coli (FPC)**
- Genetic defect of Adenomatous polyposis coli (APC).
- APC gene located on the long arm of chromosome 5 (5q21).
- APC gene is a tumor suppressor gene.

2. Gardener's syndrome: Polyposis coli, Multiple Osteomas, Epidermal cysts and Fibromatosis
3. Turcot syndrome: Polyposis coli, Glioma and Fibromatosis

Malignant tumors of intestine

Adeno-carcinoma

- The most common malignancy of the GI tract. **Mostly rectum or sigmoid colon**
- **Predisposing factors**

1. IBD, adenomas, polyposis syndrome.
2. Diet appears to play an important role in the risk for colon cancer: Low fibre diet, High fat content, Alcohol, Reduced intake of vit A, C & E:

- **Carcinogenesis:** two pathogenetically distinct pathways for the development of colon cancer:

1. **The APC/B-catenin pathway (85 %):** Hereditary mutation of the APC gene is the cause of **familial adenomatous polyposis (FAP)** which lead to colon cancer.
2. **The DNA mismatch repair genes pathway:** Five DNA mismatch repair genes (MSH2, MSH6, MLH1, PMS1, AND PMS2), give rise to the **hereditary non polyposis colon carcinoma (HNPCC) syndrome.**

Colorectal Carcinoma

- Left-sided carcinomas early symptoms of obstruction and frank bleeding
- Right-sided carcinomas Iron deficiency anemia.
- **Tumor marker for assessment of recurrence: CEA carcinoembryonic antigen**

Carcinoid tumors

- Neoplasms arising from endocrine cells found along the length of GIT mucosa.
- **Morphology**: Ultrastructural features: neurosecretory electron dense bodies in the cytoplasm.
- **Clinical features:** Asymptomatic, may cause obstruction, intussusception or bleeding, and may elaborate hormones: Zollinger-Ellison, Cushing's carcinoid or other syndromes.
- **Carcinoid syndrome:** Paroxysmal flushing, episodes of asthma-like wheezing, right-sided heart failure, attacks of watery diarrhea, abdominal pain, The principal chemical mediator is serotonin.
  The syndrome is classically associated with ileal carcinoids with hepatic metastases.

Lymphoma

- Most often low-grade lymphomas arising in mucosal-associated lymphoid tissue (MALT) lymphoma or high-grade non-Hodgkin's lymphomas of B cell type.
- May occur in any part of the intestine;
- The ileocecal region is a favored site for Burkitt's lymphoma.

Quiz

Q1: Juvenile polyps occur in children in which of the following structures?

A) Stomach
B) Sigmoid colon
C) Rectum
D) Ascending colon

Q2: Which of the following is true about Peutz-Jehgers syndrome:

A) Autosomal recessive
B) Increase risk of developing Glioblastoma
C) Common
D) Autosomal dominant

Q3: The most prominent feature of adenomas:

A) Granuloma
B) Occur mainly in small bowel
C) Only familial cases
D) Dysplasia

Q4: Which of the following gene loss can lead to cancer?

A) MSH8
B) Chromosome 10
C) p53
D) MLH9

Q5: Right-sided Colorectal carcinoma usually present with:

A) Iron deficiency anemia
B) obstruction
C) Annular cricling lesions
D) Frank bleeding

Q6: Common presentation between Gardener's syndrome and Turcot syndrome:

A) Epidermal cysts
B) Multiple osteomas
C) Polyposis coli
D) Gliomas

Q7: The most common malignancy of the GI tract:

A) Colorectal
B) Adenocarcinoma
C) Lymphoma
D) Carcinoid

Q8: Carcinoid syndrome related to which of the following:

A) Ach
B) Norepinephrine
C) Histamine
D) Serotonin

Q9: Defect in which of the following genes can lead to Familial polyposis coli (FPC)?

A) P53 located on the short arm of chromosome 5 (5p21)
B) P53 located on the long arm of chromosome 5 (5q21)
C) APC gene located on the long arm of chromosome 5 (5q21)
D) APC gene located on the short arm of chromosome 5 (5p21)

1.C 2.D 3.D 4.C 5.A 6.C 7.B 8.D 9.C

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THANK YOU