Small and Large Intestinal pathology, part 3

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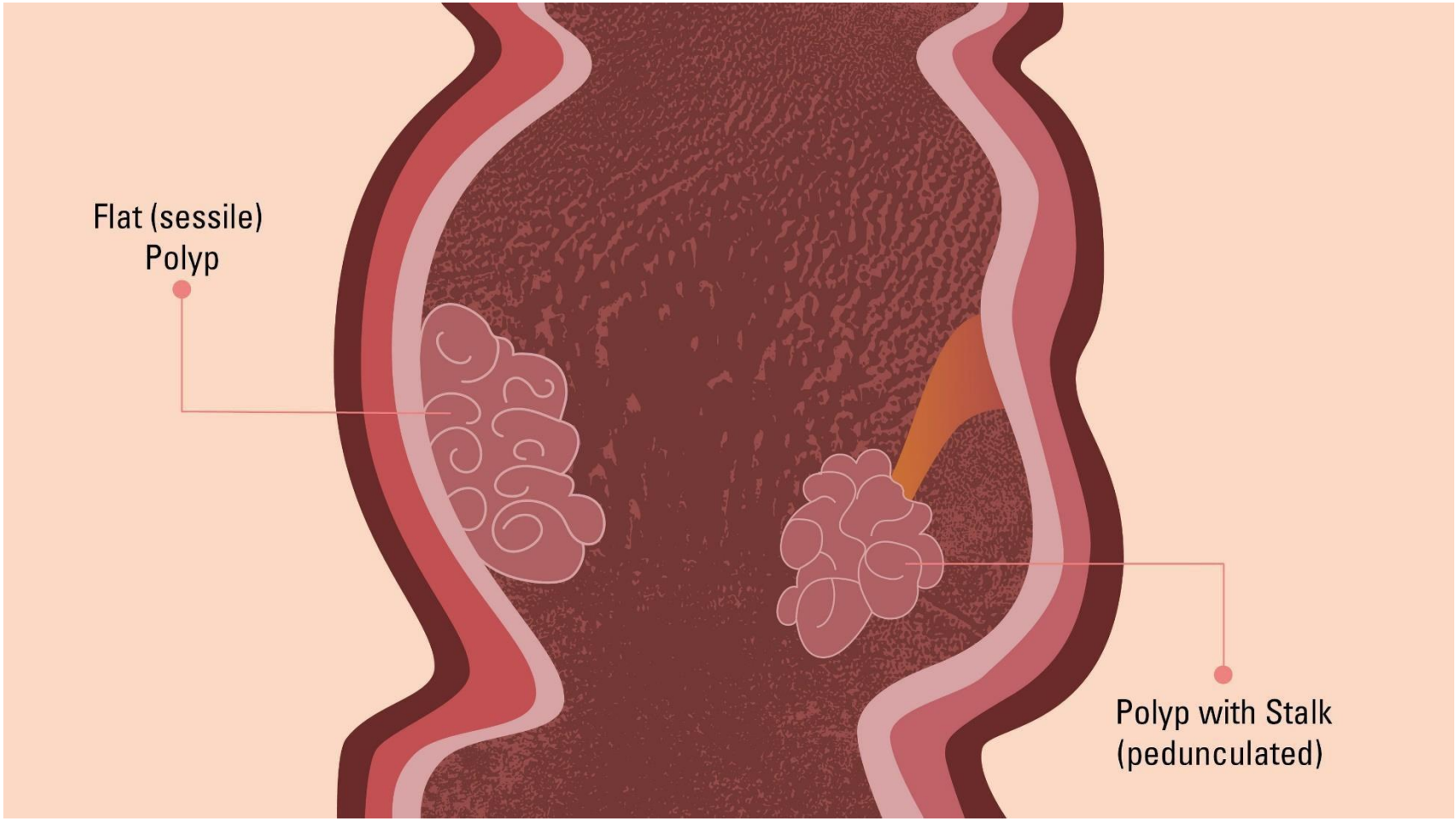
Diseases of the intestines

- 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



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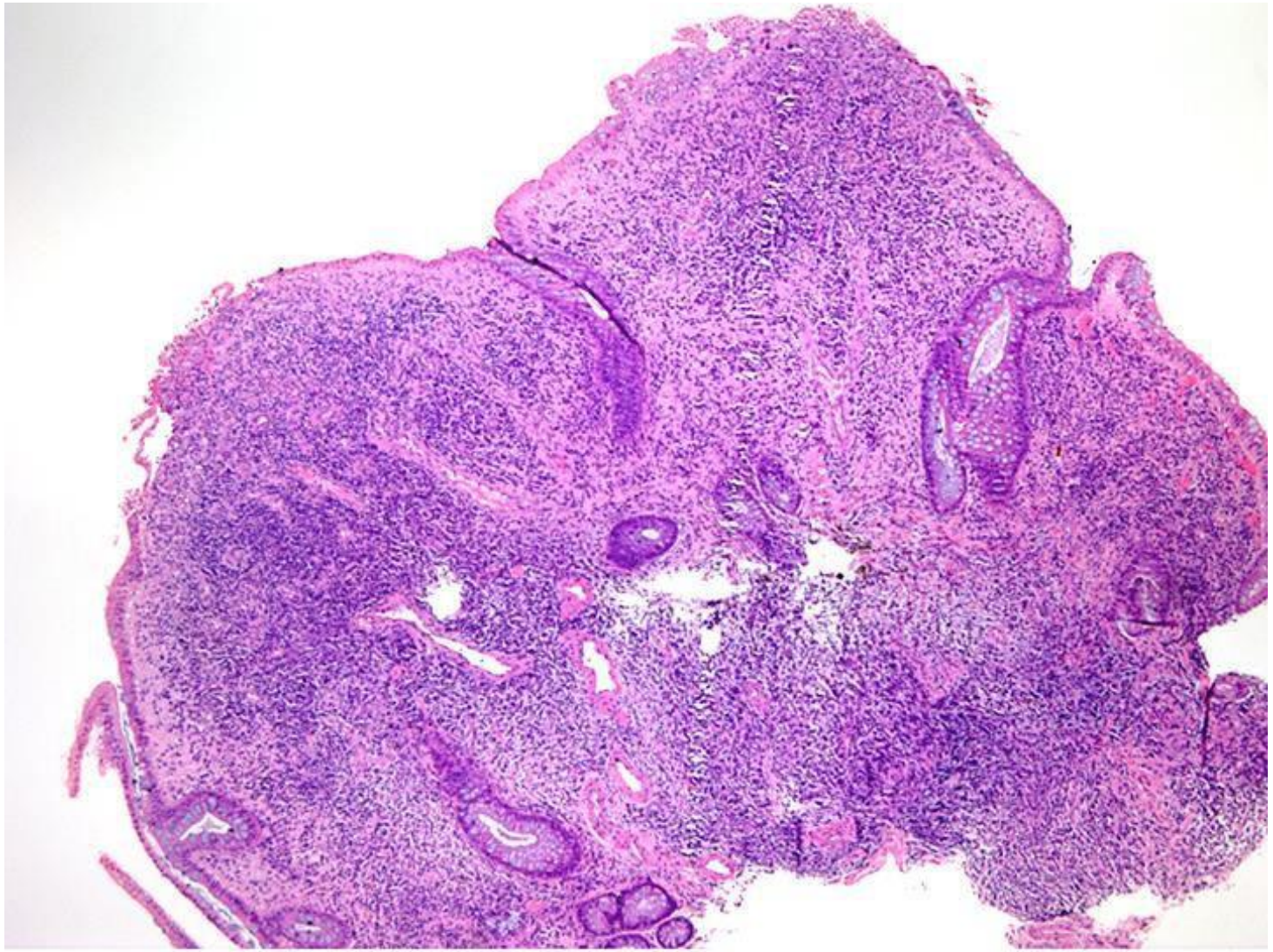
Inflammatory Polyps with surface ulceration or erosion.

uc site? left ← Rectum sigmoid

- *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.



4x: low power, dense inflammation in lamina propria

Hamartomatous Polyps

↳ normal tissue disorganized in same location.
MC site ? Lung

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

- Juvenile Polyps
- Peutz-Jeghers Syndrome

Juvenile Polyps

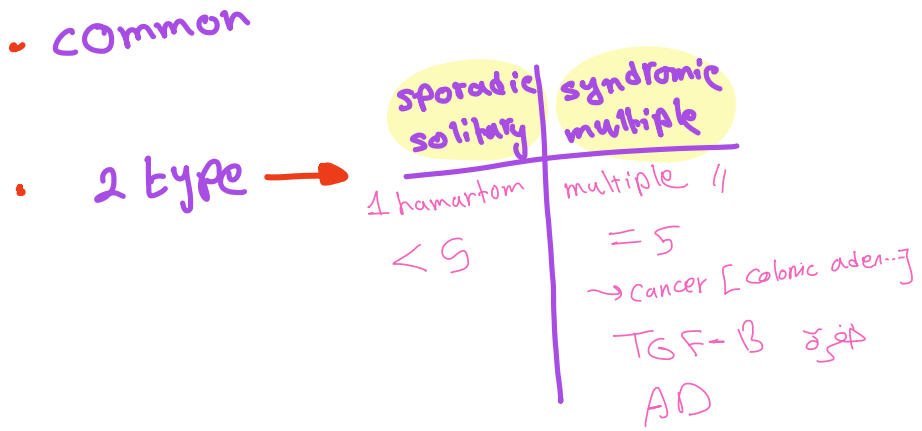
- Most common hamartomatous polyp

- **Sporadic are solitary.**

Children younger than 5 years of age
Rectum.

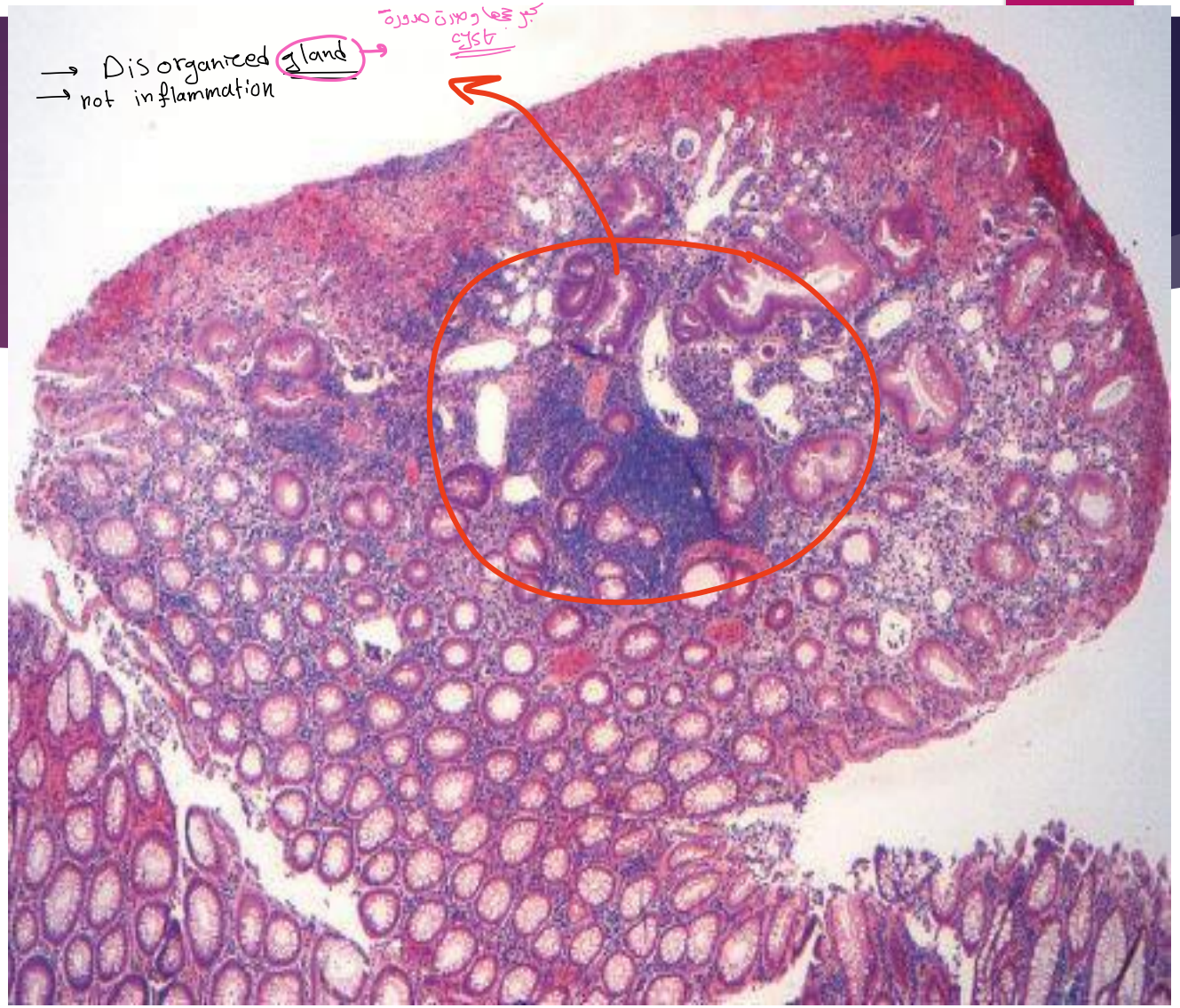
- **Syndromic are multiple.**

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.

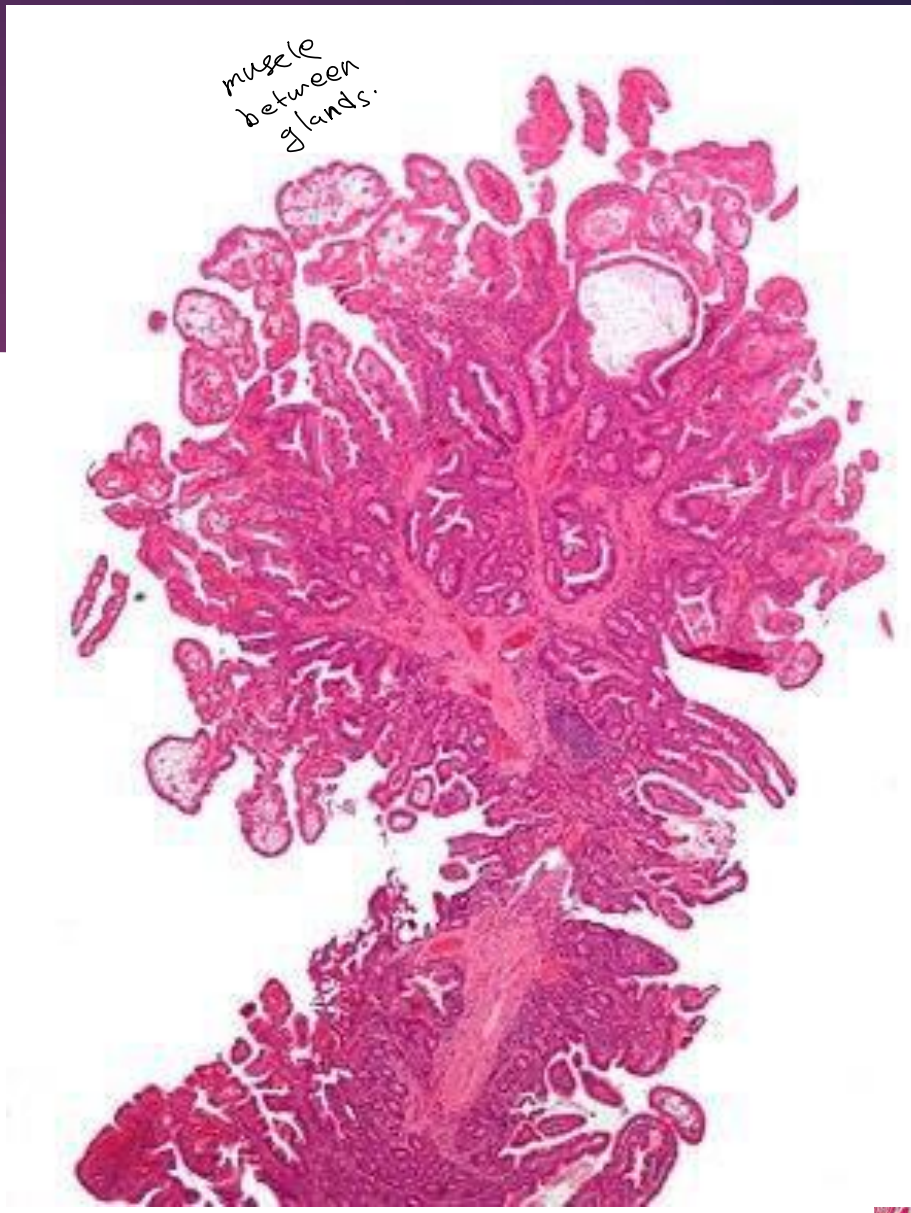


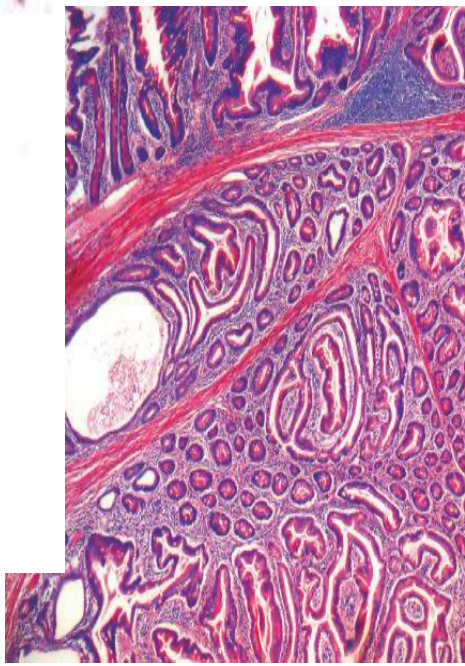
Peutz-Jeghers Syndrome

- 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.





Mucocutaneous pigmentation

Hyperplastic Polyps

- Common
- 5th-6th decade. 50 - 60 y
- Decreased epithelial turnover and delayed shedding of surface epithelium >>> pileup of goblet cells & epithelial overcrowding
- **No malignant potential** → Eso

Hyperplastic polyp

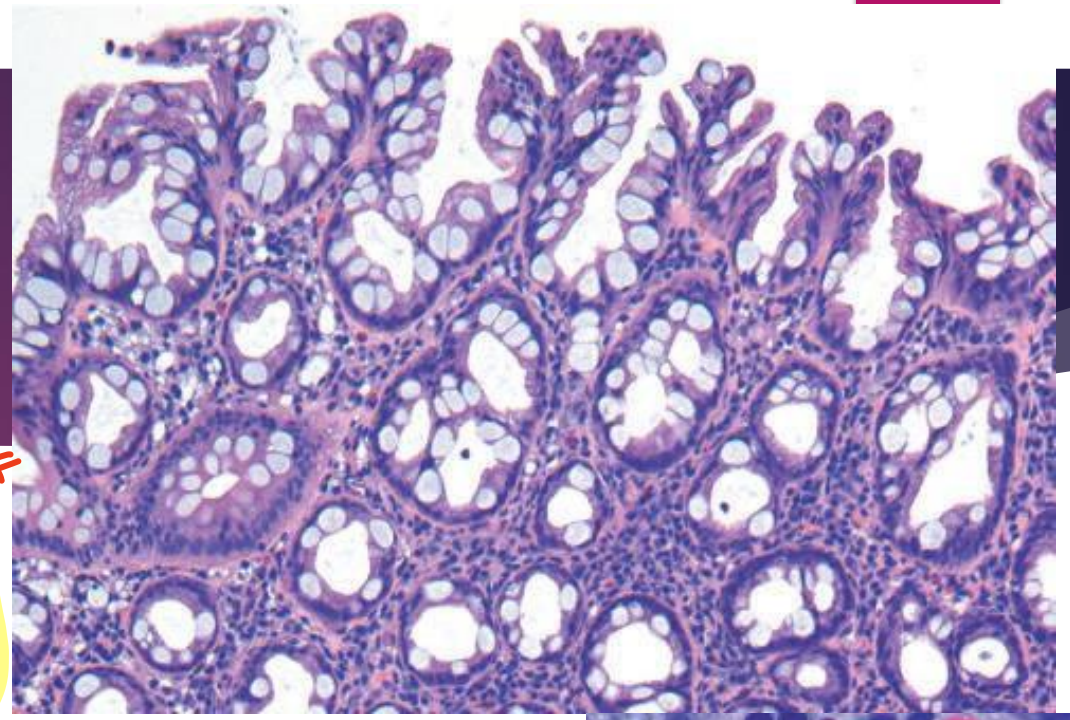
exam

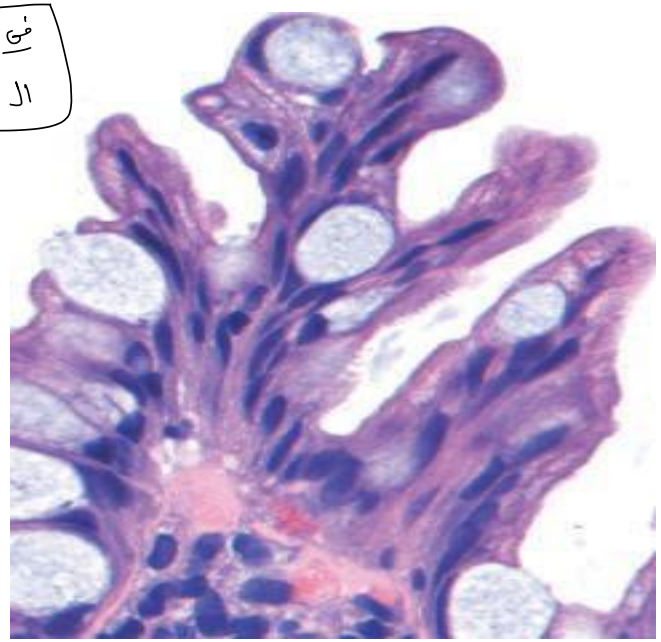
- Left colon
- Rectosigmoid.
- Small < 5 mm
- Multiple

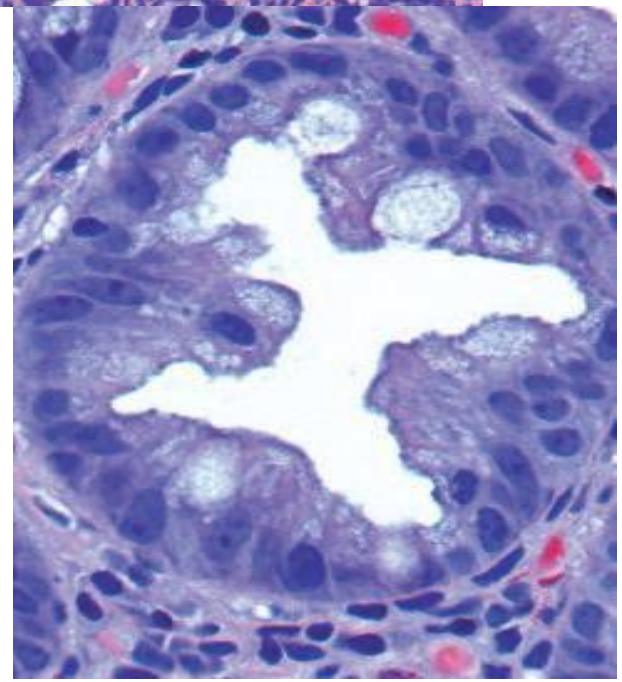
- Crowding of goblet & absorptive cells.

اول ماشوف زيادة في goblet cell
دغري تكون هاي hyperplastic polyp

polyp Adenoma في ال goblet cell بقل عددهم

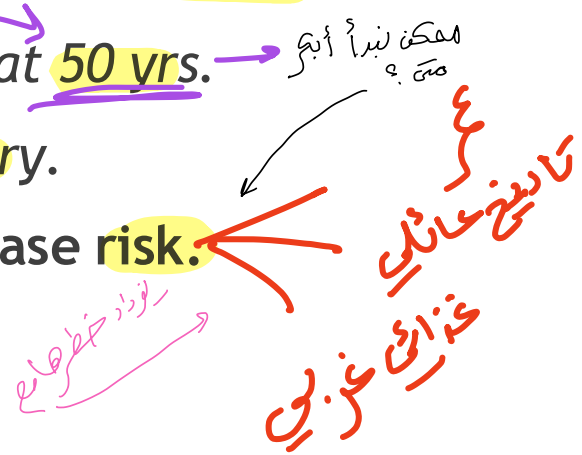




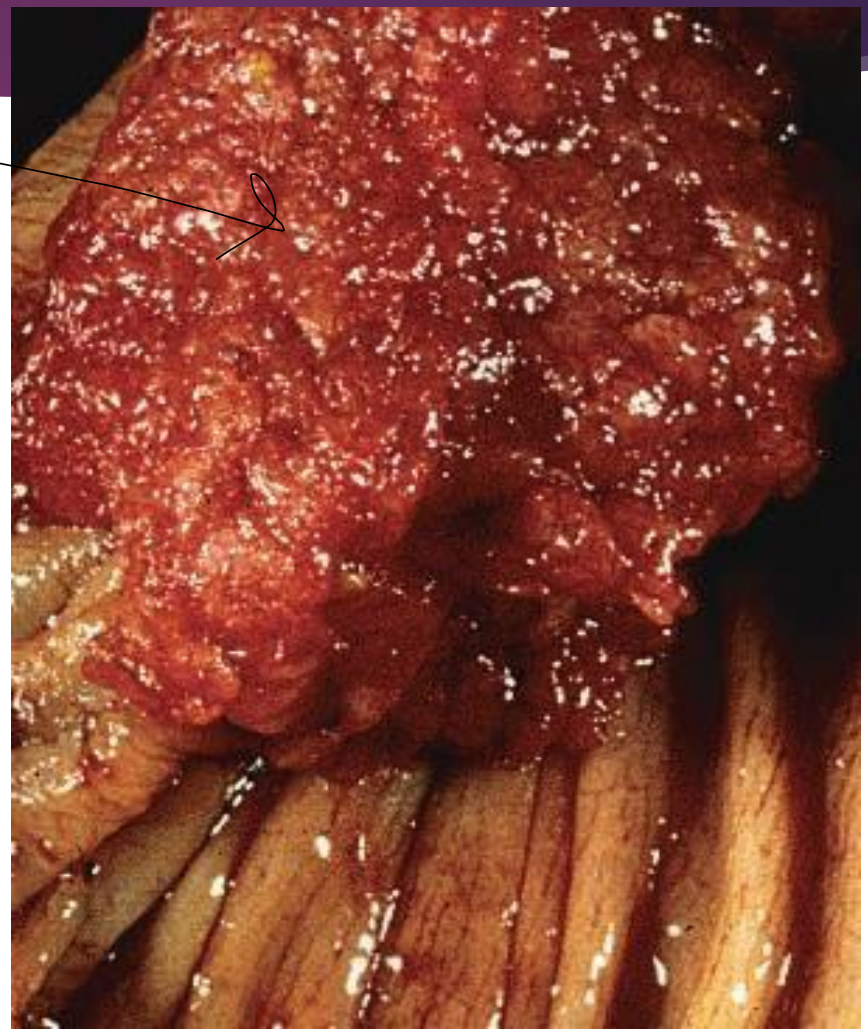


Adenomas

- 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

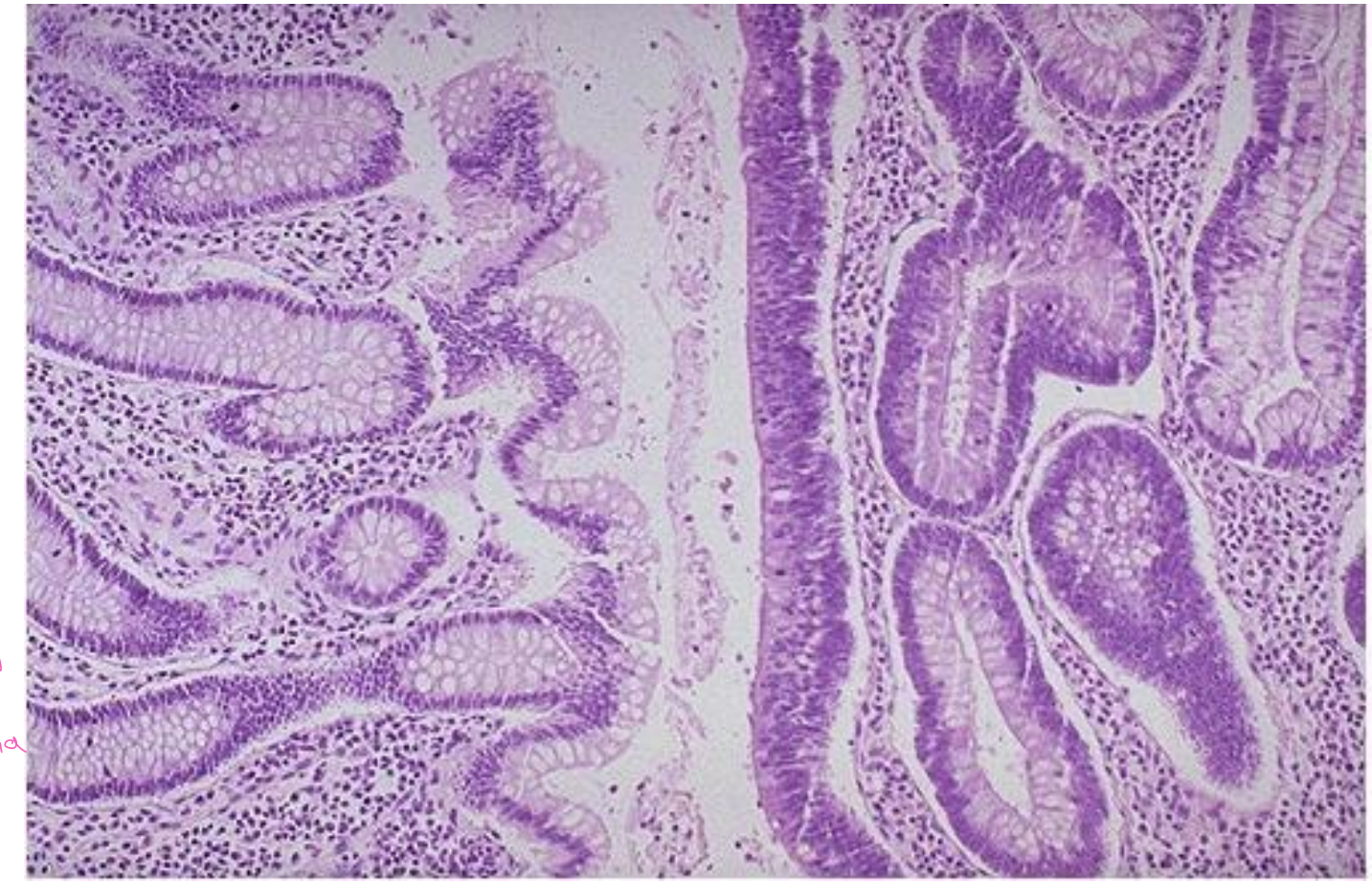


Colon adenoma

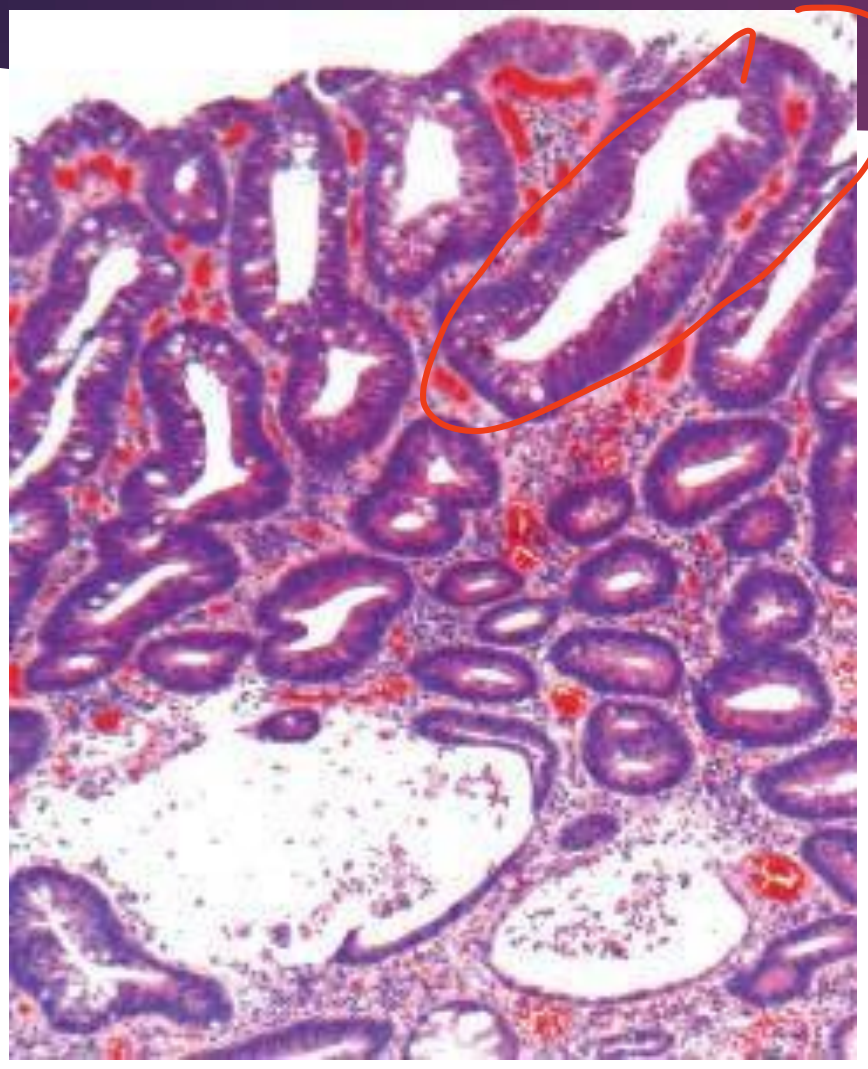
→ 3 types: Tubular, villous, mix [Tubulovillous]

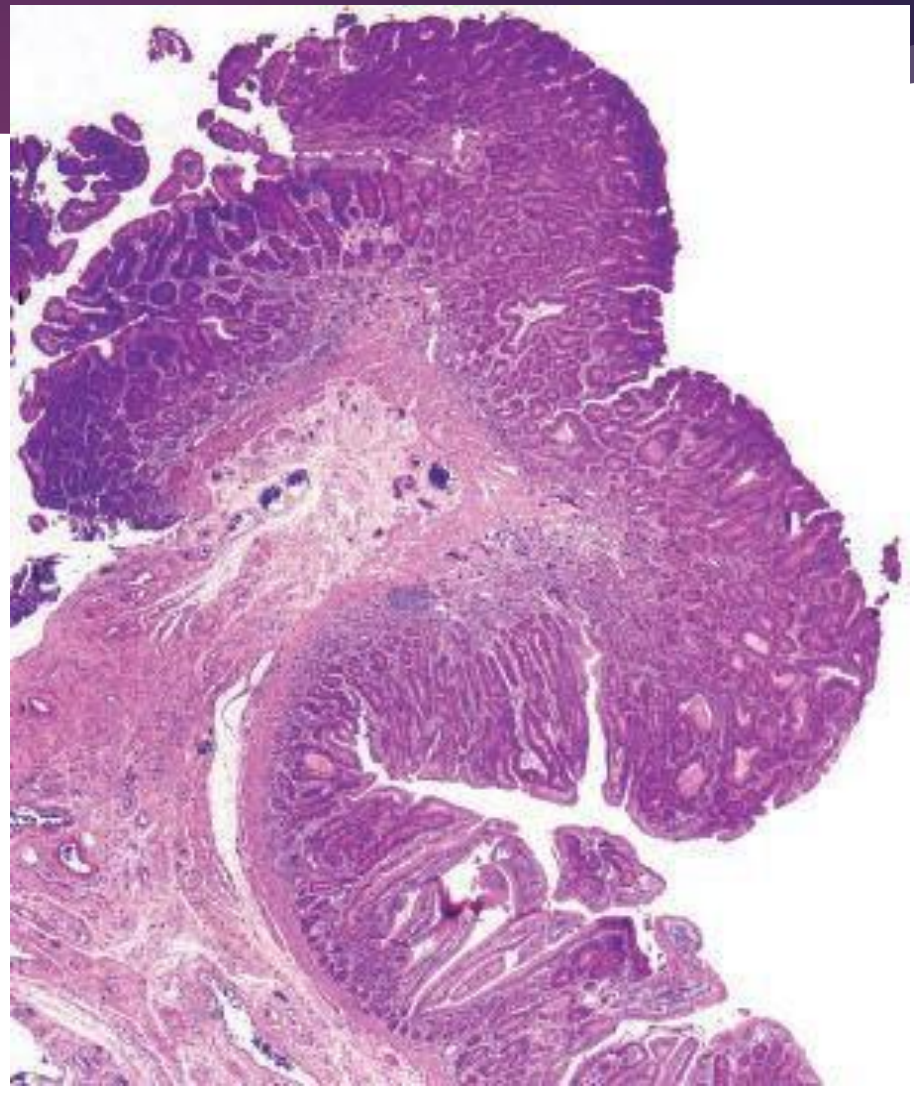
- **Hallmark: epithelial dysplasia**
- **Dysplasia**: nuclear hyperchromasia, elongation, stratification, high N/C ratio.
- **Size**: most important correlate with risk for malignancy
- **High-grade dysplasia is the second factor**

cancer ← polyp (likelihood)
1 size
2 high grade dysplasia

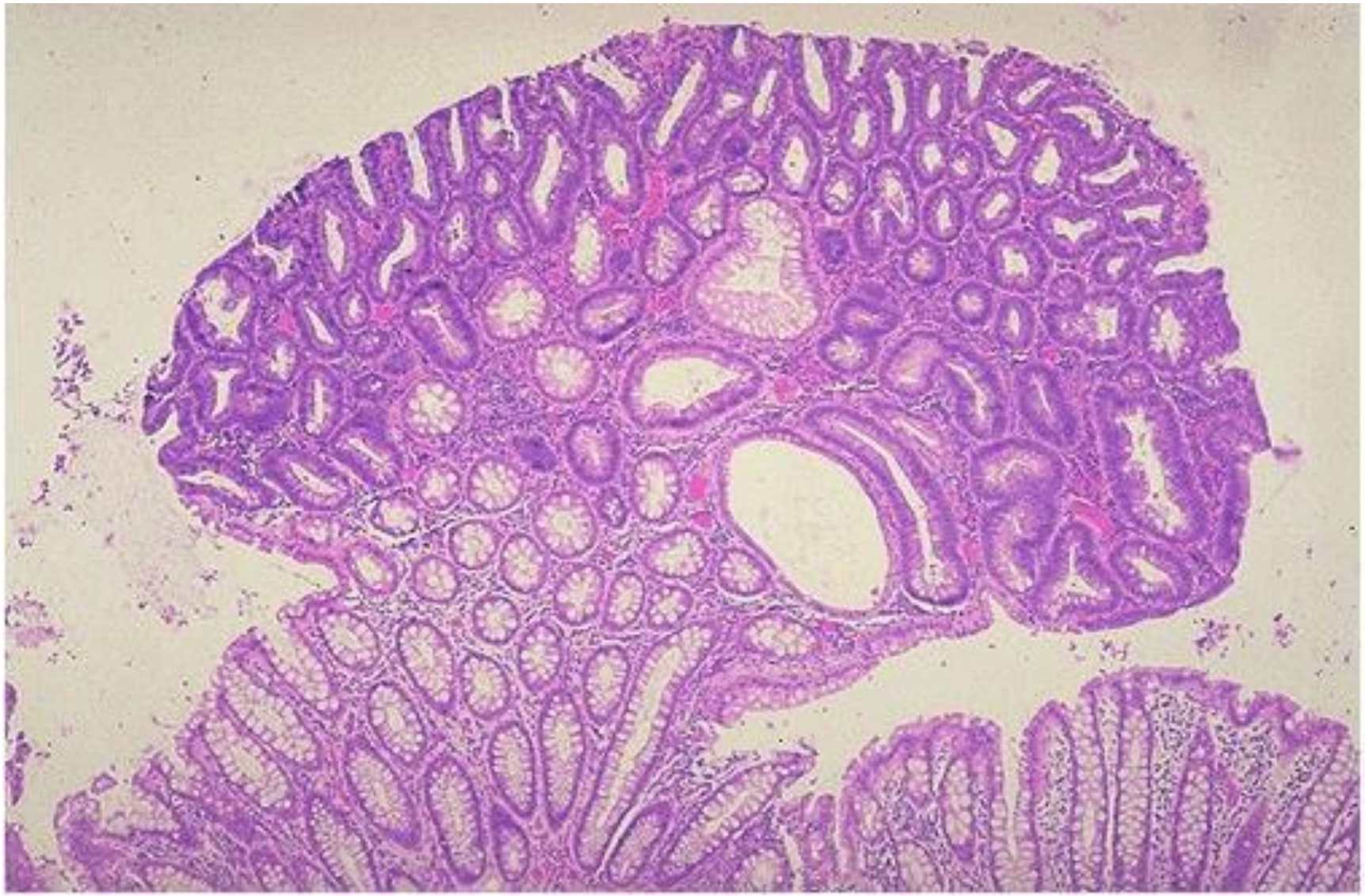


Tubular adenoma

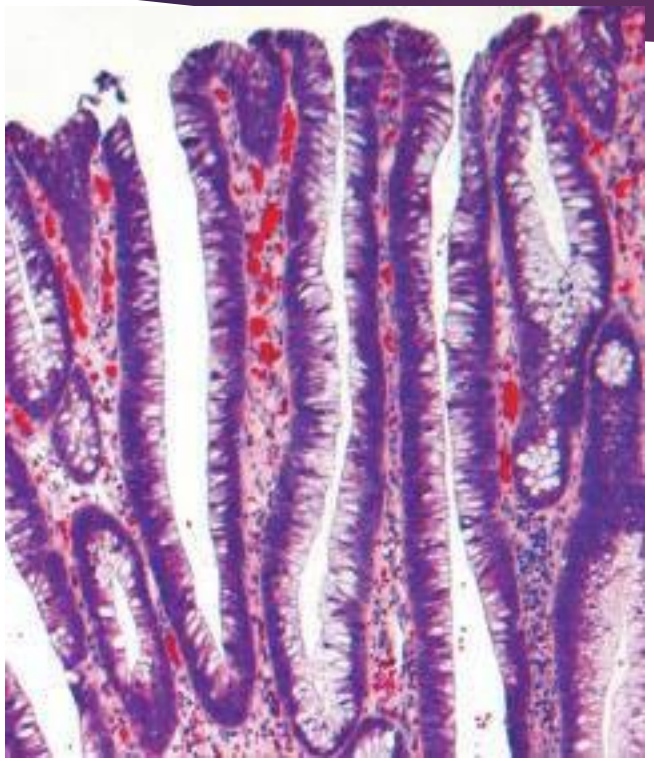




Tubular

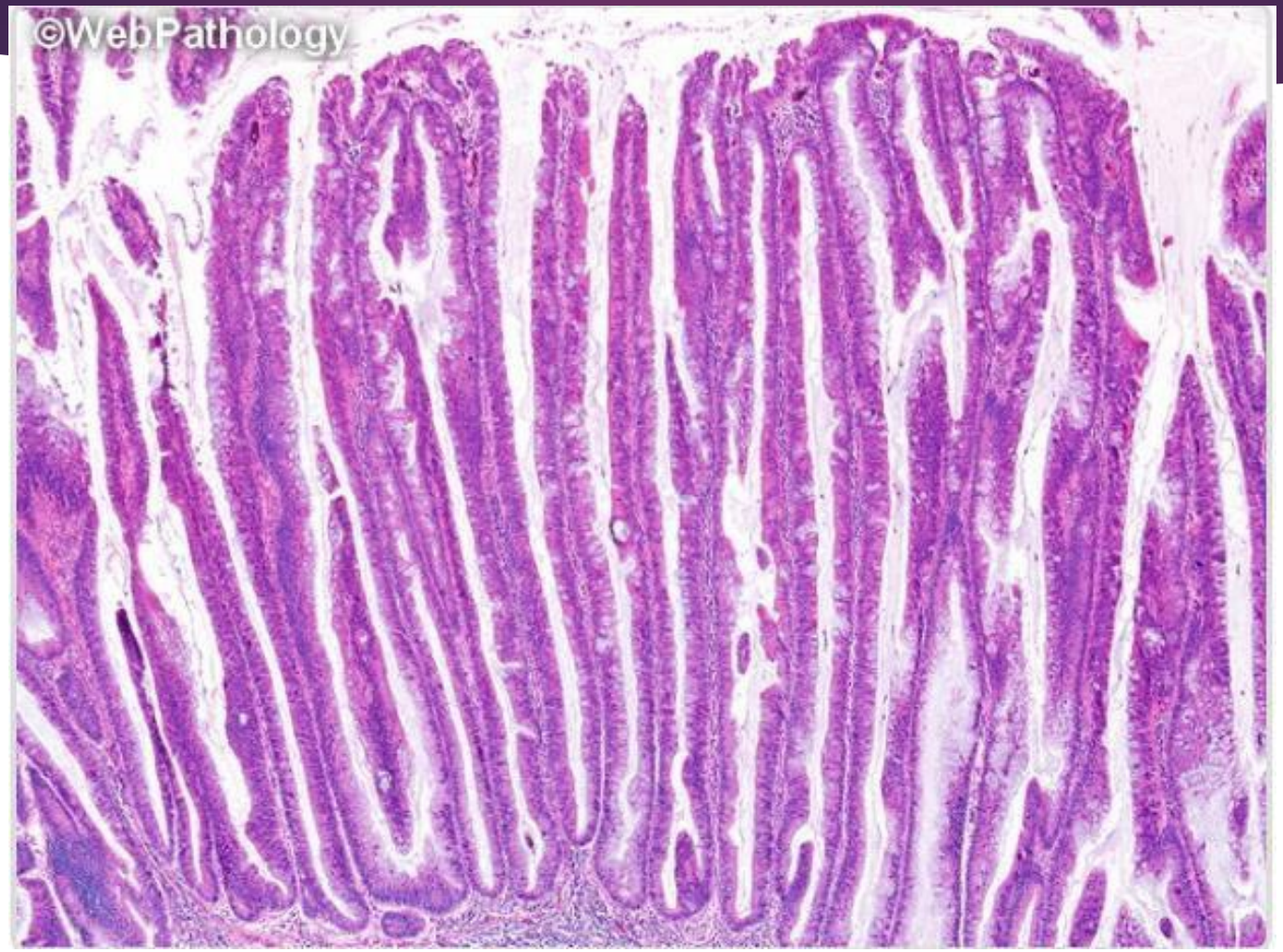


Villous adenoma.



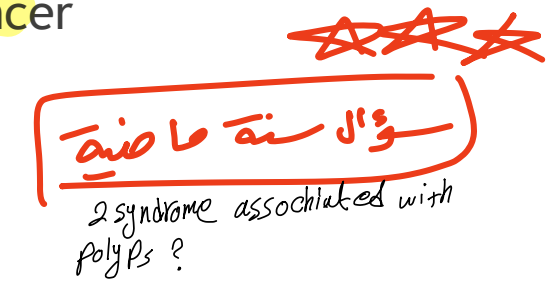
- Long slender villi.
- More frequent invasive foci
- **Architecture:**
- **Tubular.**
- **Tubulovillous.**
- **Villous.**

Villous adenoma



Familial Syndromes

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



- **Familial Adenomatous Polyposis (FAP)**
- **Hereditary Nonpolyposis Colorectal Cancer (HNPCC)**

Familial adenomatous polyposis FAP

associated with other tumor

- 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*,

AD
Familial
100 polyp
cancer in colon 100%
Tx: prophylactic colonectomy
Adenomatous polyp

- Variants of FAP: Gardner syndrome and Turcot syndrome.

Adenoma with CNS cancer

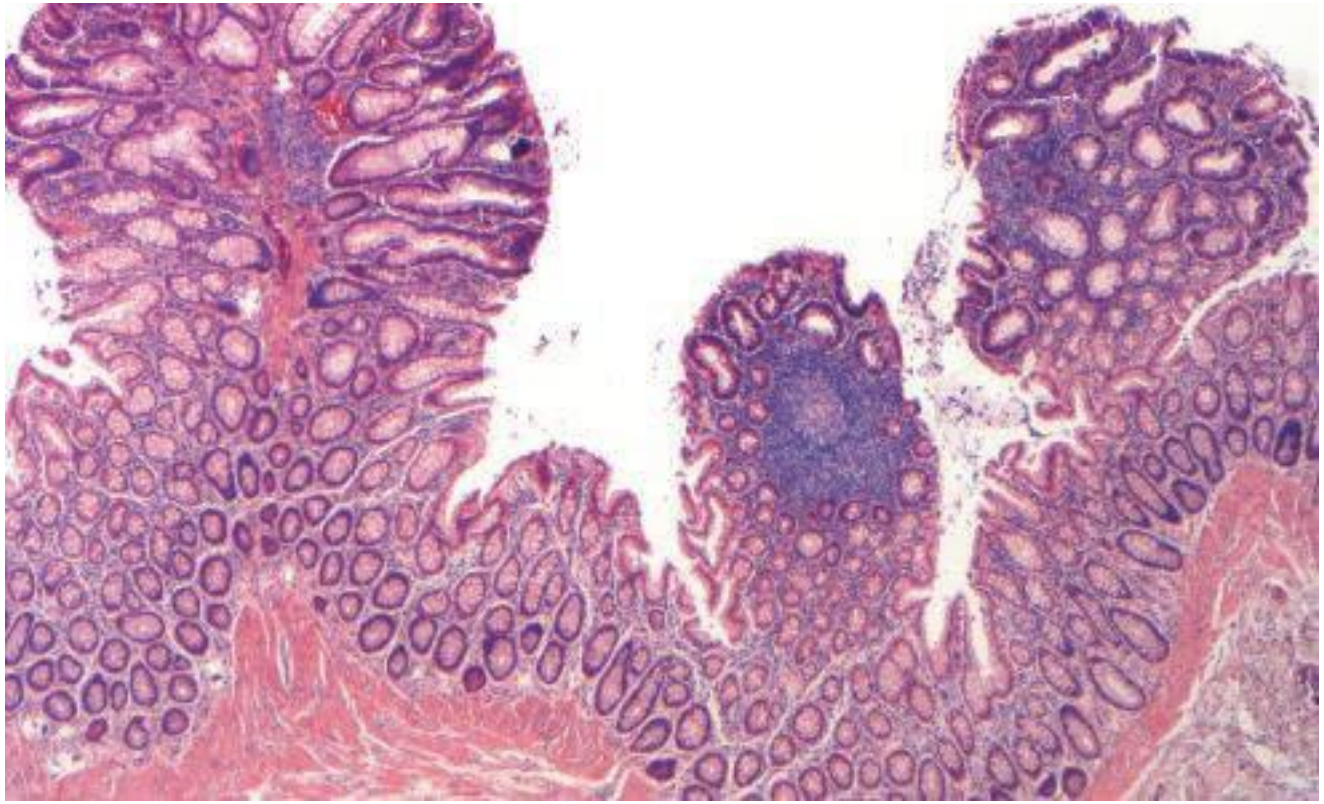
- **Gardner syndrome**: intestinal polyps + osteomas (mandible, skull, and long bones); epidermal cysts; desmoid and thyroid tumors; and dental abnormalities. أكياس جلدية
- **Turcot syndrome**: intestinal adenomas and CNS tumors (medulloblastomas >> glioblastomas)

FAP

multiple polyp

Dysplasia مع

100 of Adenamatus polyp.



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.

exam

not FAP

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/ß-catenin pathway >> increased WNT signaling**
- **Microsatellite instability pathway >> defects in DNA mismatch repair**

- Stepwise accumulation of multiple mutations

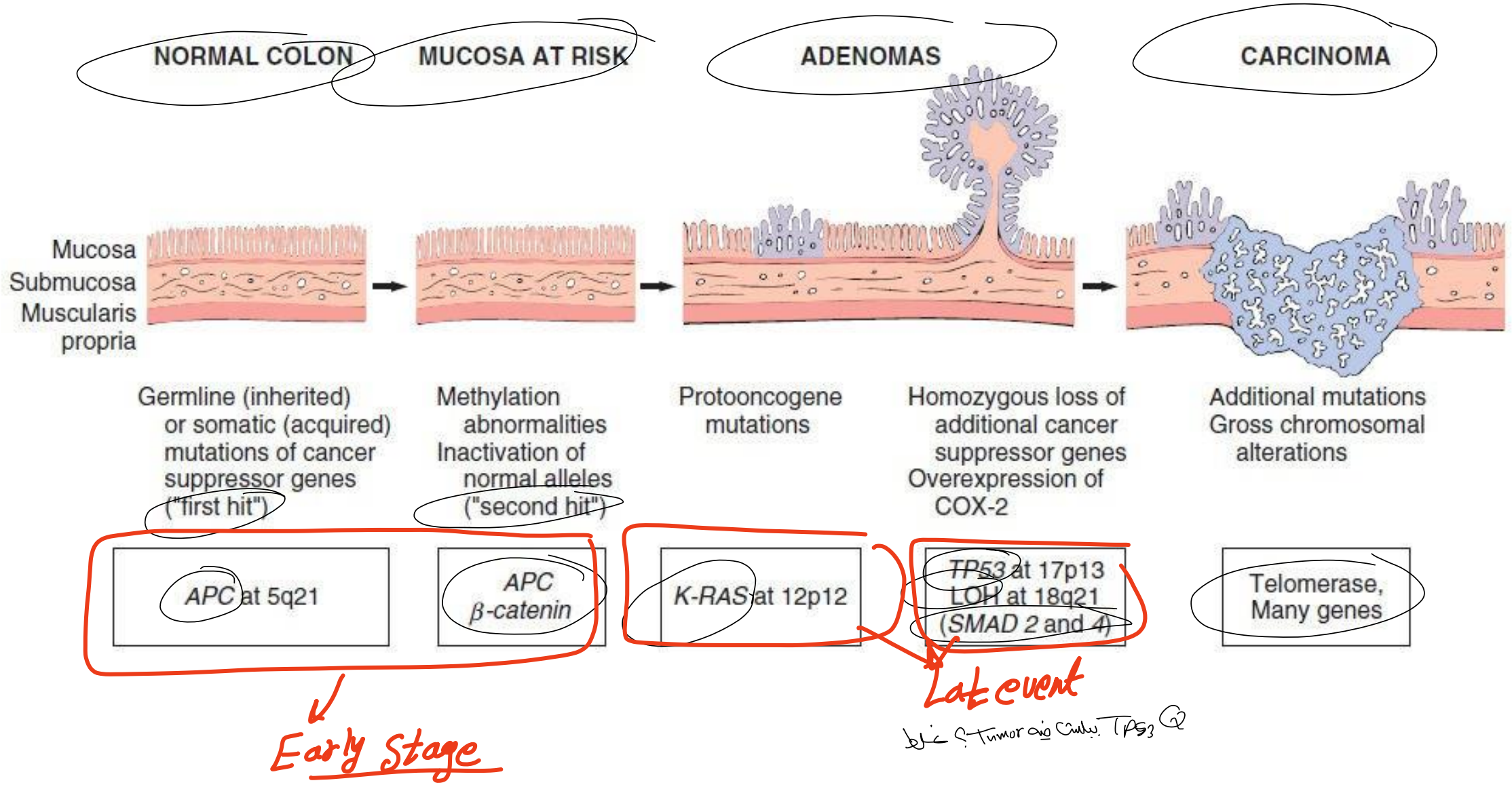
The APC/B-catenin pathway: chromosomal instability

- **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 B-catenin, a component of the WNT signaling pathway.*
- *Both copies of APC should be inactivated for adenoma to develop (1st and 2nd 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.

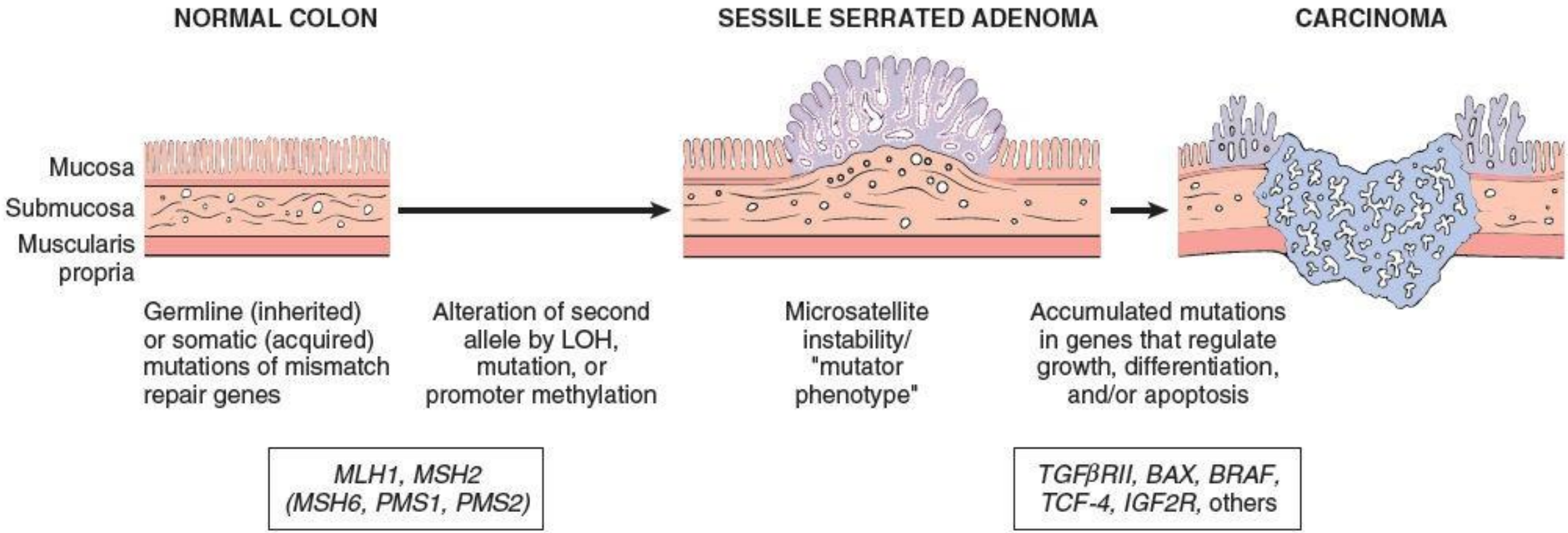
malignant


NORMAL COLON
MUCOSA AT RISK
ADENOMAS
CARCINOMA
Mucosa
Submucosa
Muscularis propria
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
APC at 5q21
APC
β-catenin
K-RAS at 12p12
TP53 at 17p13
LOH at 18q21
(SMAD 2 and 4)
Telomerase,
Many genes
Early Stage
Late event

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
SESSILE SERRATED ADENOMA
CARCINOMA
Mucosa
Submucosa
Muscularis propria
Germline (inherited) or somatic (acquired) mutations of mismatch repair genes
Alteration of second allele by LOH, mutation, or promoter methylation
Microsatellite instability/ "mutator phenotype"
Accumulated mutations in genes that regulate growth, differentiation, and/or apoptosis
MLH1, MSH2 (MSH6, PMS1, PMS2)
TGFβRII, BAX, BRAF, TCF-4, IGF2R, others

Etiology	Molecular Defect	Target Gene(s)	Transmission	Predominant Site(s)	Histology
Familial adenomatous polyposis (70% of FAP)	APC/WNT pathway	*APC*	Autosomal dominant	None	Tubular, villous; typical adenocarcinoma
Hereditary nonpolyposis colorectal cancer HNPCC	DNA mismatch repair	*MSH2, MLH1*	Autosomal dominant	Right side	Sessile serrated adenoma; mucinous adenocarcinoma
Sporadic colon cancer (80%) most	APC/WNT pathway	*APC*	None	Left side	Tubular, villous; typical adenocarcinoma
Sporadic colon cancer (10%–15%)	DNA mismatch repair	*MSH2, MLH1*	None	Right side	Sessile serrated adenoma; mucinous adenocarcinoma

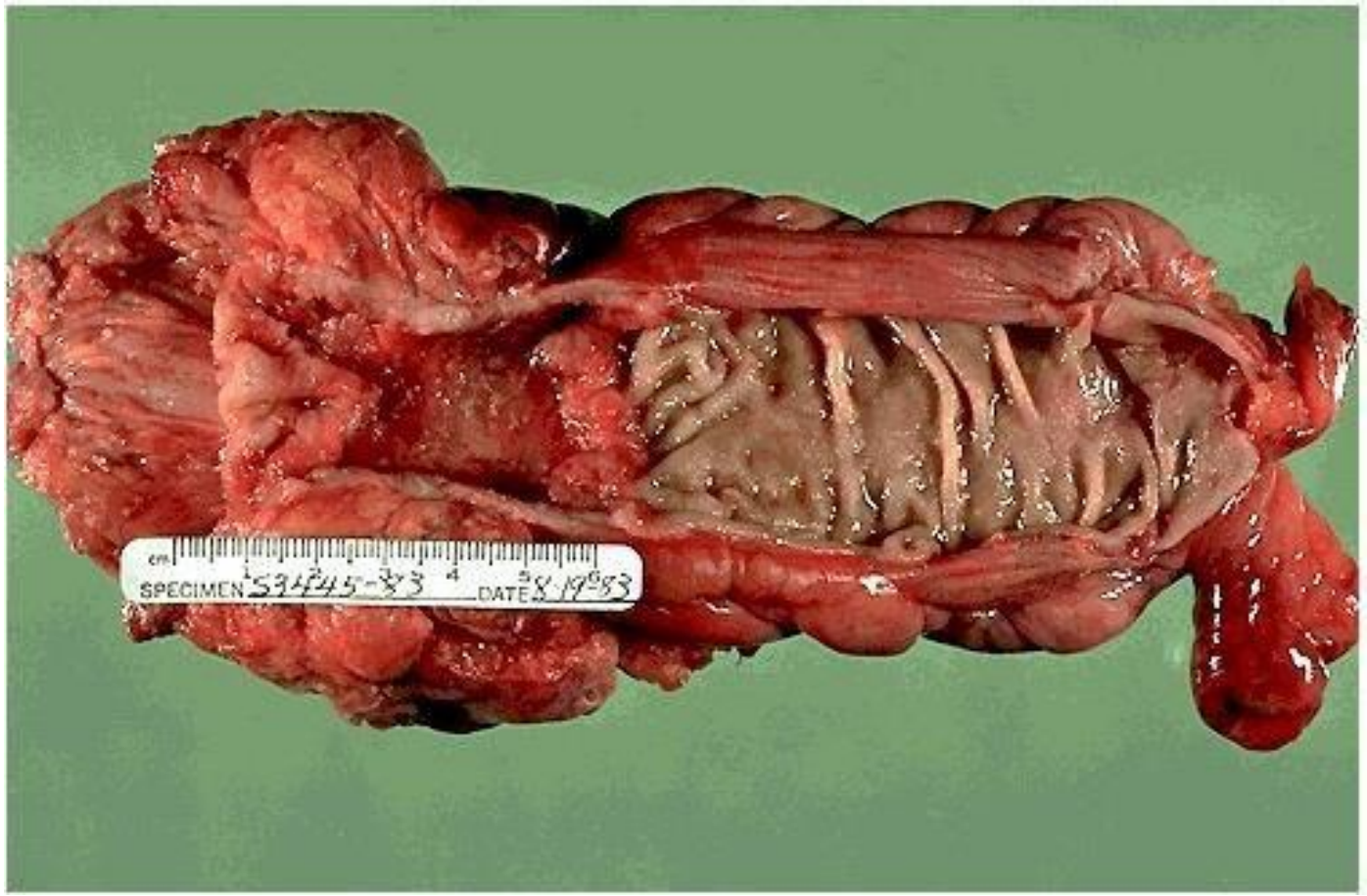
MORPHOLY

- Macroscopic:
- Proximal colon tumors: polypoid, exophytic masses
- Proximal colon: rarely cause obstruction.
- Distal colon: annular lesions “napkin ring” constrictions & narrowing

حلقية

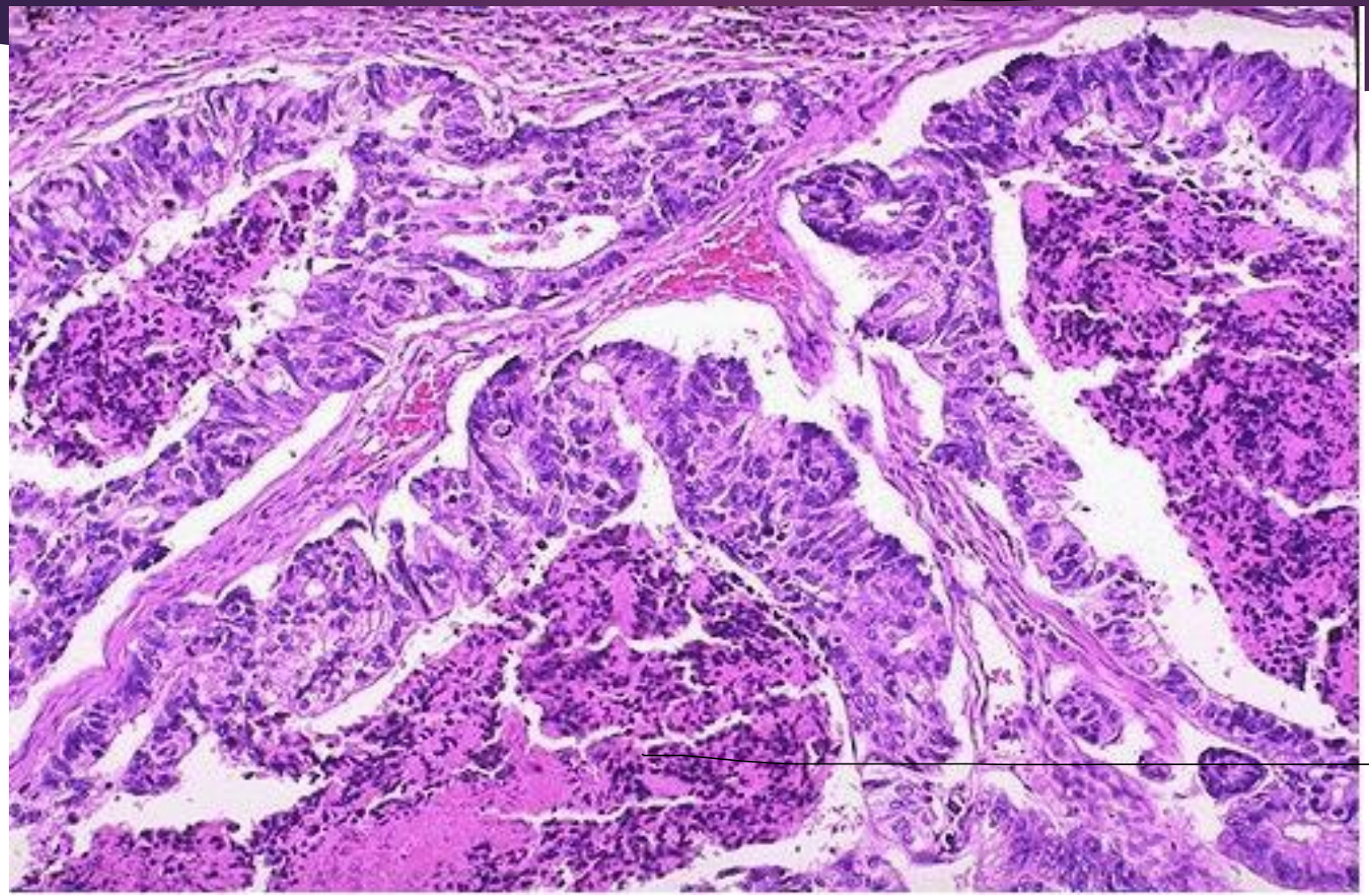
- Microscopic:
- Dysplastic GLANDS with strong desmoplastic response.
- Necrotic debris are typical.
- Some tumors give abundant mucin or form signet ring cells.

Rectosigmoid adenocarcinoma, napkin ring R side



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.

→ not obstruction
Due to lumen of Right side is large.
لومن القولون الأيمن واسع

→ ✓ obstruction so → constipation
Due to lumen of left side is narrow.

يخرج في الإخراج

- Poor differentiation and mucinous histology >> poor prognosis

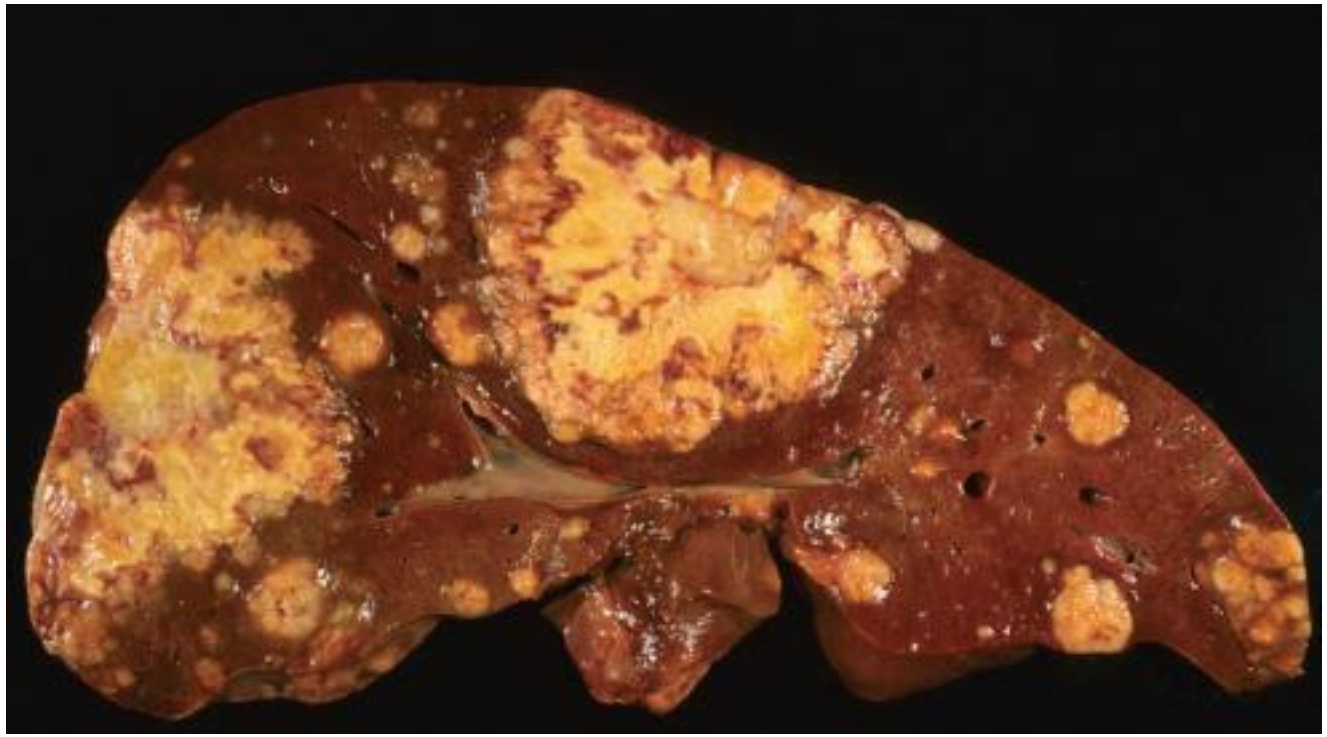
- ***Most important two prognostic factors are***

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: Different Diagnosis

Mesenteric lymphadenitis,
Acute salpingitis,
Ectopic pregnancy,
Mittelschmerz (pain associated with ovulation),
Meckel diverticulitis.

MC cause of Acute Appendicitis is ?

→ Fecalith → stool صلب

- 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.** فيه Abscess
- **Acute gangrenous appendicitis >> necrosis and ulceration.**

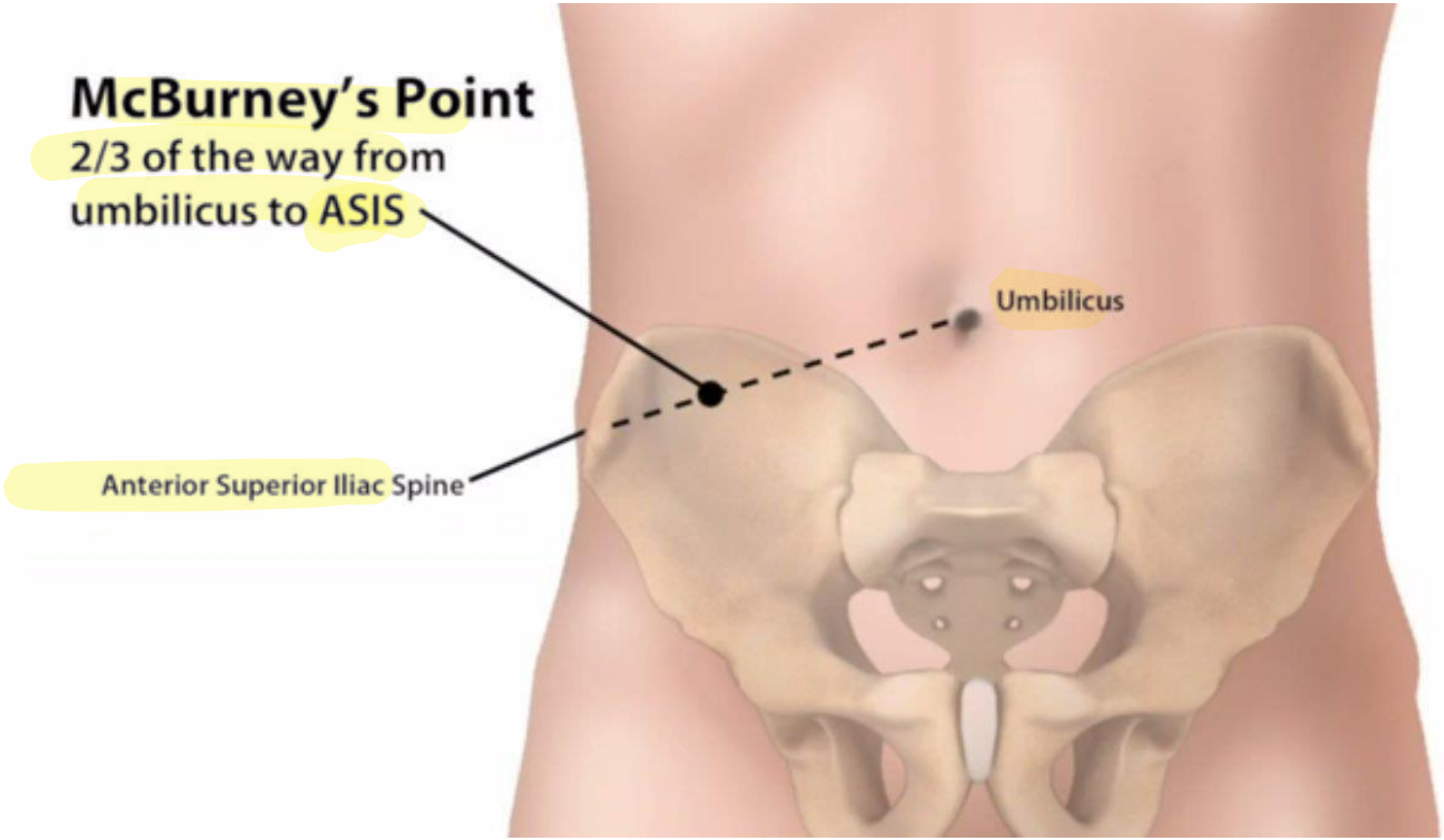
أنواع زايدة

فيه ثقب

Clinical Features

- Early acute appendicitis: periumbilical pain
- Later: pain localizes to the right lower quadrant,
- Nausea, vomiting, low-grade fever, mildly leukocytosis.

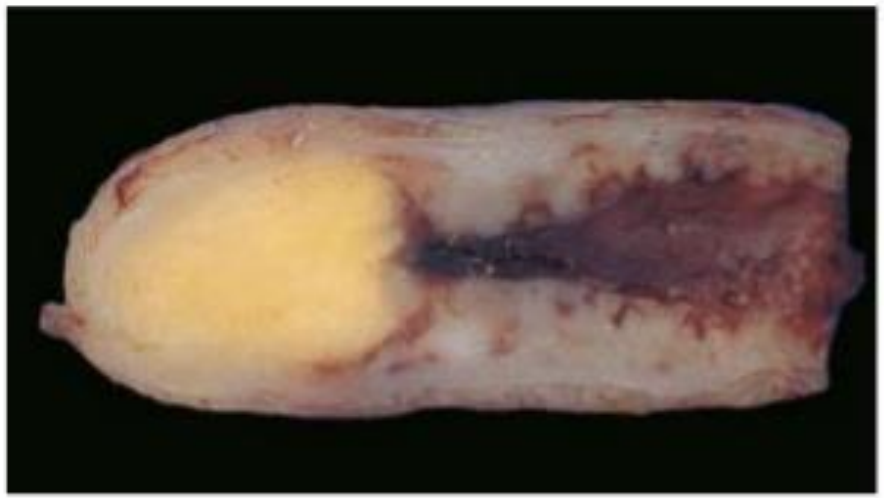
  A classic physical finding is ***McBurney's sign*** (McBurney's point).
- Signs and symptoms are often absent, creating difficulty in clinical diagnosis.


McBurney's Point
2/3 of the way from umbilicus to ASIS
Umbilicus
Anterior Superior Iliac Spine

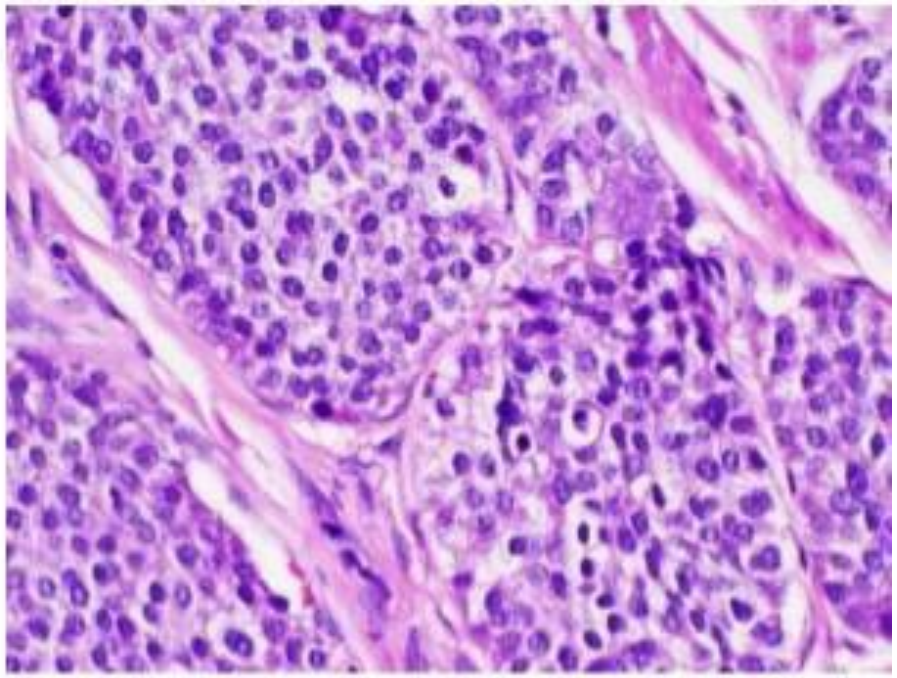
TUMORS OF THE APPENDIX

- **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