GIS

Sheet no. 7

Pathology

Done by: Bilal Al-hamaideh.

Correction: Sham Al-Salim.

Doctor: Manar hijjer.

In this sheet we will complete our journey in small intestine disease, specially in Crohn Disease and Ulcerative Colitis :
Let's go عزيزي القارئ الجميل :

Clinical Features (CD) :

- Intermittent attacks ("on and off" disease):
  - of mild diarrhea, low-grade fever, and abdominal pain.
  - Most common complain .
- Acute right lower-quadrant pain and fever (20%) :
  - Due to terminal ileitis or ileocecal valve inflammation.
  - It may be the first manifestation of the disease and may be misdiagnosed as acute appendicitis. If the surgeon were to try to remove the appendix, they would find it normal but the terminal ileum is inflamed.
- Bloody diarrhea and abdominal pain: (colonic involvement).
- Asymptomatic intervals between attacks: (weeks to months of no symptoms).
- Triggers of the attacks:

physical or emotional stress, specific dietary items, NSAID use, and cigarette smoking.
(**they are not causes of the disease!)**.

Long-Term Complications:

- Iron-deficiency anemia Accompanied with
  1) a long history of bloody diarrhea.
  2) Malabsorption due to destruction in the small intestine.

- Hypoproteinemia and hypoalbuminemia :
  - malabsorption of nutrients, vitamin B12 and bile salts (as the disease affects the small bowel in 70% of cases).

o Most prominently is malabsorption of vitamin B12 and bile salts as they are absorbed in the terminal ileum, which is what's most commonly affected by the disease.

- Fistulas, peritoneal abscesses
  - (complication of rupture and resultant peritonitis), and strictures due to fibrosis. The patient may come complaining of constipation as a new symptom.

• Most feared complication is Risk of colonic adenocarcinoma:

- The risk is increased when the disease continues for many years.
- It would not appear after only a year, but as the disease is sometimes diagnosed late, you should always suspect this risk and follow up with the patient with multiple colonoscopies. This should be done even if the patient is being treated and does not complain of symptoms.

***Sometimes the disease is diagnosed late with the emergence of long-term complications as the patient will not seek treatment with intermittent abdominal pain**. So screening is pretty important.

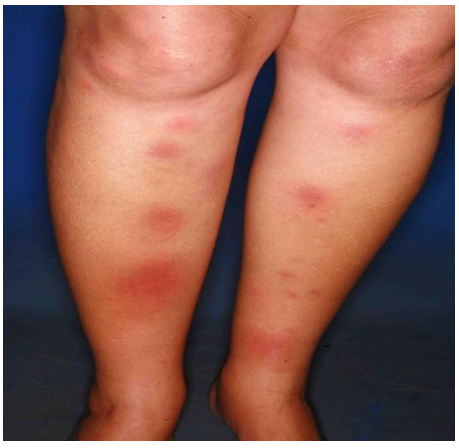
Extra-Intestinal Manifestations:

The patient will not complain only of gastric problems because it is an immune-mediated, multi-system disease.

• Uveitis : Inflammation of the iris.
• Migratory polyarthritis : Multiple joints at the same time or one after the other. joint is affected by immune-mediated arthritis: swelling, redness, and pain.

• Sacroiliitis : Inflammation of the sacroiliac joint.
• Ankylosing spondylitis : Immune-mediated disease of the spine.
• Erythema nodosum.
• Clubbing of the fingertips.
• Primary sclerosing (more with UC) :
A disease affecting the bile ducts in the liver, causing fibrosis and narrowing of the duct. This leads to elevated levels of bilirubin and jaundice.

This image depicts erythema nodosum.
They are red, elevated, and tender lesions that appear mainly on the lower limbs.

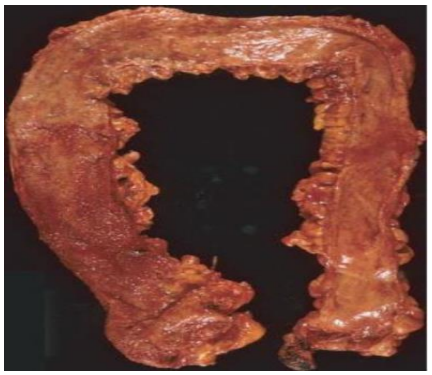


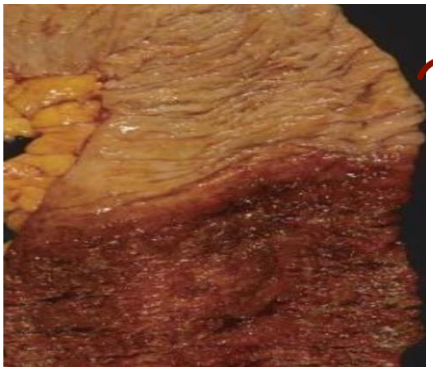
Ulcerative Colitis:

Morphology:

• Always involves the rectum : Can check for involvement through colonoscopy or biopsy
• Extends proximally in continuous pattern – No skip lesions.
• Pan colitis : The entire large intestine (up to the cecum) is affected.
But this does not occur in all of the cases.
• Occasionally focal appendiceal or cecal inflammation - In a discontinuous fashion, large area of the colon is skipped and there is only focal appendiceal or cecal inflammation.But this is not the typical scenario.
• It may be ulcerative proctitis (only the rectum is involved) or ulcerative proctosigmoiditis (rectum and sigmoid colon are the only involved segments).
• Small intestine is normal (except-in cases of pan colitis-in backwash ileitis, where a very small area {only a few cm} of the terminal ileum is affected by the regurge of inflammatory infiltrate through the ileocecal valve). **In general, if we have small and large intestinal involvement we should think of Crohn's disease.**

Pan colitis:-

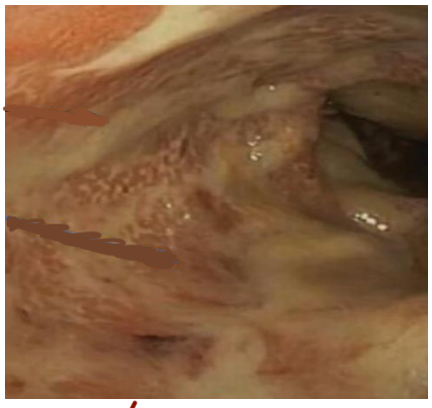




Note:- No skip lesion.

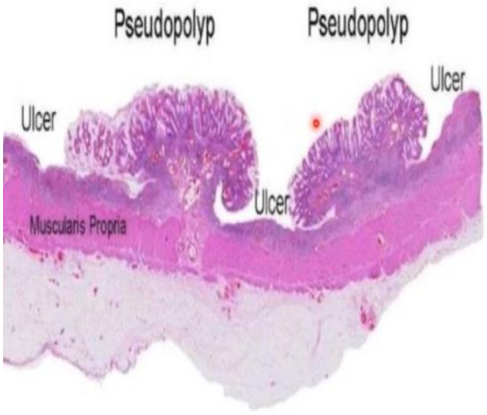
Clinical Features:

• Relapsing remitting disorder : On and off disease.
• Attacks of bloody mucoid diarrhea + lower abdominal cramps followed by an asymptomatic interval and then another attack.
• Attacks of pain are temporarily relieved by defecation.
• Attacks last for days, weeks, or months before the patient enters an asymptomatic interval.
• Infectious enteritis may trigger disease onset.
For unknown reasons, cessation of smoking may trigger the disease symptoms as well.
• Colectomy cures intestinal disease only.
So extra-intestinal manifestations (which still can be seen in UC) are not cured by colectomy.

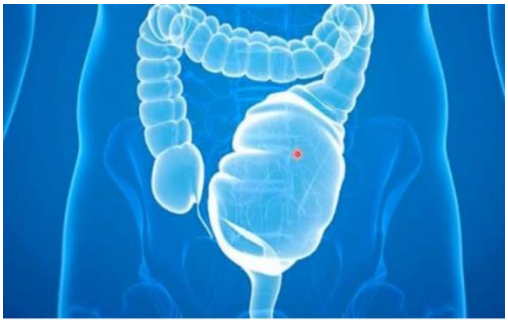


Mucopurulent material and ulcers.
"Because of pus"

Macroscopic:

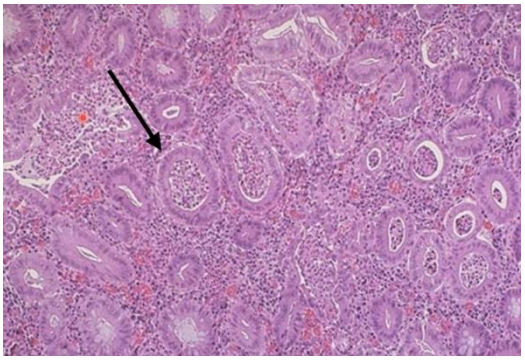


• Broad-based ulcers – Not deep, serpentine, or linear. They are shallow ulcers that usually affect the mucosa and submucosa.
• Pseudopolyps – Elevated, unaffected area between ulcers (however, the mucosa is inflamed with no ulcer). Not true polyps.
• Mucosal atrophy: occurs in long-standing disease.
• Mural thickening absent : The wall of the bowel is atrophic and thin
• Serosal surface normal: No transmural inflammation
• No strictures
• **Complication:** Toxic megacolon
– Due to the thinning of the bowel wall. If the patient develops a concurrent infection, the gases produced by the bacteria may lead to dilation of the colon. This is known as toxic megacolon, which has the risk of rupture, sepsis, perforation and resultant peritoneal inflammation. Can also be seen in CD and other inflammatory conditions of the colon (like pseudomembranous colitis) so it's not specific.



Microscopic:

The microscopic changes in UC are not specific, as a similar appearance can be seen in CD.
• Inflammatory infiltrate – Whether it is active or chronic inflammation.
• Crypt abscesses : Seen in the active phase.
• Crypt distortion : A chronic feature with haphazard arrangement of colonic crypts.
• Epithelial metaplasia – Another chronic feature
• Submucosal fibrosis – Can be seen due to inflammation, but thickening of the bowel wall is not seen in UC.
• Inflammation limited to mucosa and submucosa – No transmural inflammation.
• No skip lesions – **The disease is continuously spread from the rectum.**
• No granulomas.



This is an important table that summarizes all the changes discussed and the differences between CD and UC. Remember that the differentiation is not easy nor straightforward. Even with all forms of information collected, a definitive diagnosis may still not be reached and it is just described as chronic inflammatory bowel disease.

Feature	Crohn Disease	Ulcerative Colitis
Macroscopic		
Bowel region affected	Ileum ± colon	Colon only
Rectal involvement	Sometimes	Always
Distribution	Skip lesions	Diffuse
Stricture	Yes	Rare
Bowel wall appearance	Thick	Thin
Inflammation	Transmural	Limited to mucosa and submucosa
Pseudopolyps	Moderate	Marked (More prominent)
Ulcers	Deep, knifelike	Superficial, broad-based
Lymphoid reaction	Marked	Moderate
Fibrosis	Marked	Mild to none
Serositis	Marked	No
Granulomas	Yes (~35%)	No
Fistulas/sinuses	Yes	No
Clinical		
Perianal fistula	Yes (in colonic disease)	No (as there is no transmural inflammation)
Fat/vitamin malabsorption	Yes	No
Malignant potential	With colonic involvement	Yes
Recurrence after surgery	Common (as other areas of GIT affected)	No
~~Toxic megacolon~~	~~No~~	~~Yes~~

NOTE: Not all features may be present in a single case.

The last row regarding toxic megacolon is present in the slides but was crossed out in the video.

Colitis-Associated Neoplasia

• The risk of adenocarcinoma of the colon is increased in long standing(UC,CD)
• Begins as dysplasia which can transform into carcinoma. These patients should be followed up by regular check-up colonoscopies with random biopsies taken to check for the appearance of dysplasia

.

• **Risk (of dysplasia and subsequent carcinoma)** depends on:
o Duration of disease: Risk increases after 8-10 years.
o Extent of involvement: More risk with pancolitis.
o Inflammation : Risk increases with frequency & severity of active disease with neutrophils.

. Therefore, a patient compliant with their treatment, with a limited number of attacks, and their condition controlled by medication, will not have active inflammation and this lowers the risk of adenocarcinoma.

نهايت عاشرة = بداية عاشرة

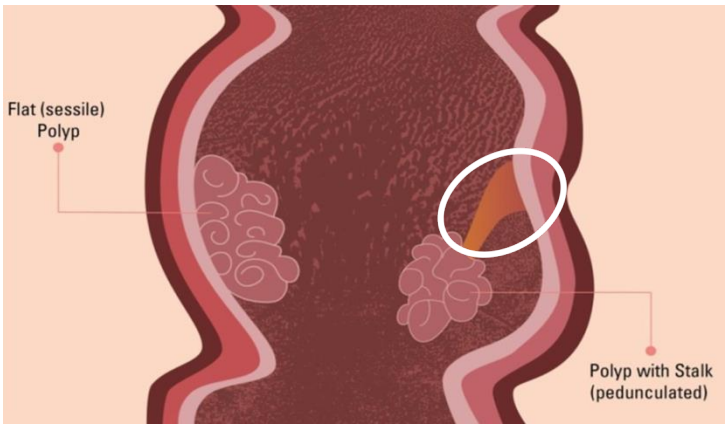
COLONIC POLYPS AND NEOPLASTIC DISEASES:

- A polyp: is an abnormal growth of tissue projecting above the level of the mucosa. most common in the colon but may occur in other sites like the stomach (gastric polyps).
- Those without stalks (dome shaped elevations) **are referred to as sessile** , and polyps with stalks are termed **pedunculate**.
- Polyps can also be classified as :

1) non-neoplastic.

Non-neoplastic colonic polyps can be further classified as :
inflammatory, hamartomatous , or hyper-plastic .

2) neoplastic (have the potential to progress to cancer), and the most common neoplastic polyp is the colonic adenoma.



← Polyps architecture (whether the polyp is sessile or pedunculated) does NOT imply its tendency to become malignant.

NOTE: NON-NEOPLASTIC POLYP DOESN'T HAVE GENETIC MUTATIONS THAT ARE ASSOCIATED WITH NEOPLASTIC POLYPS (THIS DOESN'T MEAN THAT MUTATIONS CAN'T BE FOUND IN NON-NEOPLASTIC POLYPS).

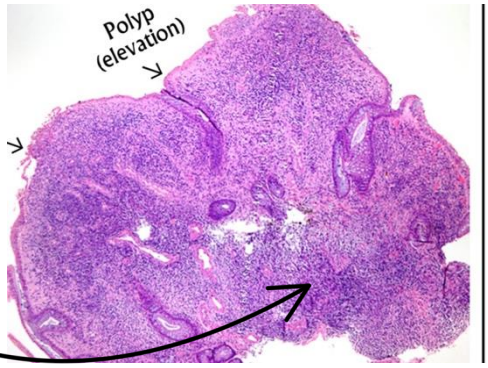
I) INFLAMMATORY POLYPS (NON-NEOPLASTIC)

Inflammatory polyps are composed of dense inflammatory cells.
The most common site where inflammatory polyps occur is the rectum, that's why we sometimes call inflammatory polyps "**solitary rectal ulcers**".
However, inflammatory polyps can be seen anywhere in the gastrointestinal tract.

- Any site that is exposed to recurrent cycles of ulceration and healing may develop inflammatory polyps.
- "Solitary rectal ulcer syndrome": involves recurrent abrasion and ulceration of the overlying rectal mucosa resulting in chronic cycles of injury and healing which produce a polypoid mass composed of inflamed and reactive mucosal tissue (inflammatory polyp).

From the picture : this is a polypoid mass with ulceration on the sides.

Notice the dense inflammatory cells.



II) HAMARTOMATOUS POLYPS (NON-NEOPLASTIC)

- Hamartomas are disorganized, tumor-like growths composed of mature cell types normally present at the site at which the polyp develops.
For exampl : in the colon, we can find a polyp that's composed of smooth muscle cells, glandular, and neural tissues surrounded by layers of mucosa and sub-mucosa forming a hamartomatous polyp.

- Hamartomatous polyps can be :
sporadic or associated with inherited syndromes (syndromic).

- The most important types of hamartomatous polyps are
1) juvenile polyps.
2) Peutz- Jeghers syndrome associated polyps.

1. JUVENILE POLYPS (Hamartomatous_Non-Neoplasmic)

* Juvenile always means young age in medicine.

- Juvenile polyps are the most common type of hamartomatous polyps. They may be sporadic or syndromic.

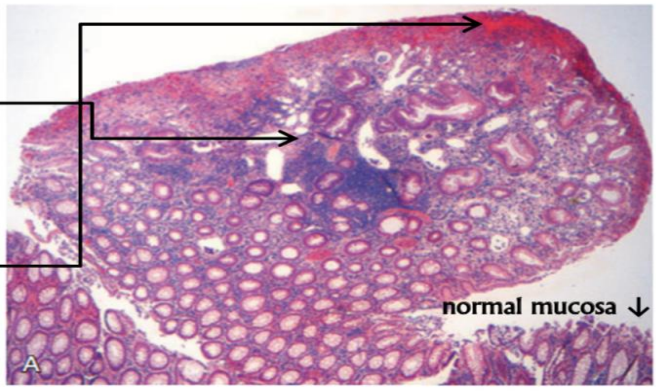
- Sporadic juvenile polyps : are usually solitary (one single polyp), and they are usually located in the rectum (like inflammatory polyps).
- juvenile polyposis syndrome is characterized by multiple polyps (syndromic polyps), the number varies from 3 to as many as 100 polyps.

  - is an autosomal dominant syndrome that is associated with mutations in pathways that regulate cellular growth, such as transforming growth factor-β (TGF-β) signaling pathway.
  - The majority of juvenile polyps (sporadic or syndromic) occur in children (hence the name "juvenile") younger than 5 years of age.

  - The juvenile polyposis syndrome is associated with an increased risk for development of adenocarcinoma within the colon and at other sites.

  - So: juvenile polyps themselves are non-cancerous, but there is an increased risk of cancer of the digestive tract in families with JPS. It's a genetic condition; this means that the risk for polyps and cancer can be passed from generation to generation in a family.

- **Juvenile polyps' morphology:**
  - ✓ Juvenile polyps are usually pedunculated$_1$ (each has a stalk) lesions that contain cystically dilated crypts (glands)$_2$, stromal granulation tissue$_3$ (on the surface), and reddish lesions$_4$ (due to the presence of inflammation) on the surface epithelium.



  - ✓ Macroscopically, they appear as large polyps with cystic spaces in between.
  - ✓ Microscopically, there are cystically dilated crypts (glands) filled with mucus, neutrophils, and debris.

2. PEUTZ-JEGHERS SYNDROME (Hamartomatous_Non-Neoplasmic):

- Peutz-Jeghers syndrome is a rare autosomal dominant disorder defined by the presence of multiple gastrointestinal hamartomatous polyps and **mucocutaneous hyperpigmentation** that carries an increased risk for development of several malignancies, including cancers of the colon, pancreas, breast, lung, ovaries, uterus, and testes.

- It's a multi-organ syndrome and ONE of its features is the presence of these hamartomatous polyps.

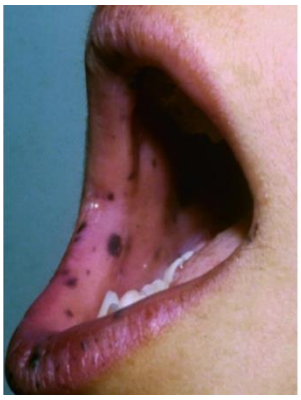
Brownish macules scattered on skin, lips and mucus membranes

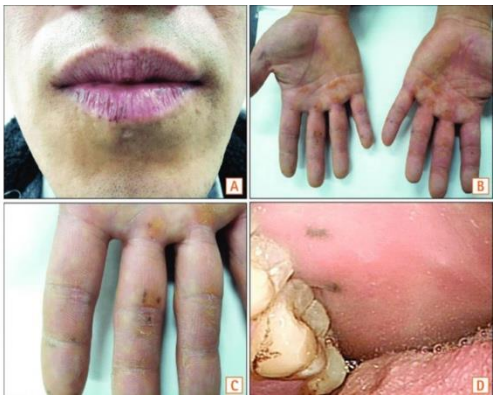
- Germ line loss of-function mutations in the LKB1/STK11gene. ← مهم للحفظ

- Intestinal polyps are most common in the small intestine.
- Mean age of patients: 10-15 y/o.

Note: Peutz-Jeghers polyps can also be sporadic but **usually they appear as syndromic.**

Macroscopically: the polyps are large and pedunculated (each has a stalk) with a lobulated contour.

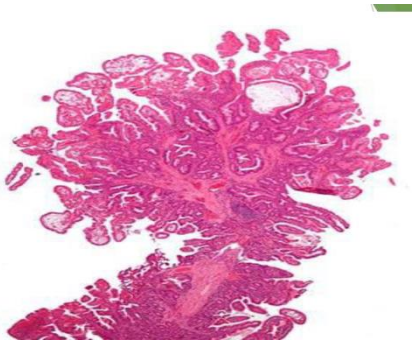


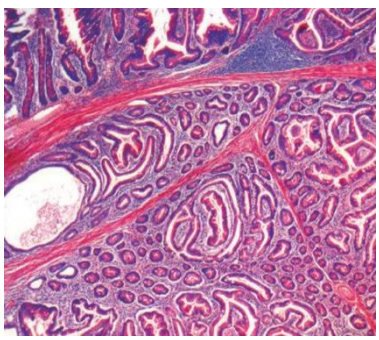


Microscopically: demonstrates a characteristic arborizing network of connective tissue, smooth muscle, lamina propria, and glands lined by normal-appearing intestinal epithelium (hamartomatous).

The center of the polyp has a Christmas tree-like branching pattern. ** very imp.

- Note: microscopic appearance does not differentiate between sporadic and syndromic forms of the disease.





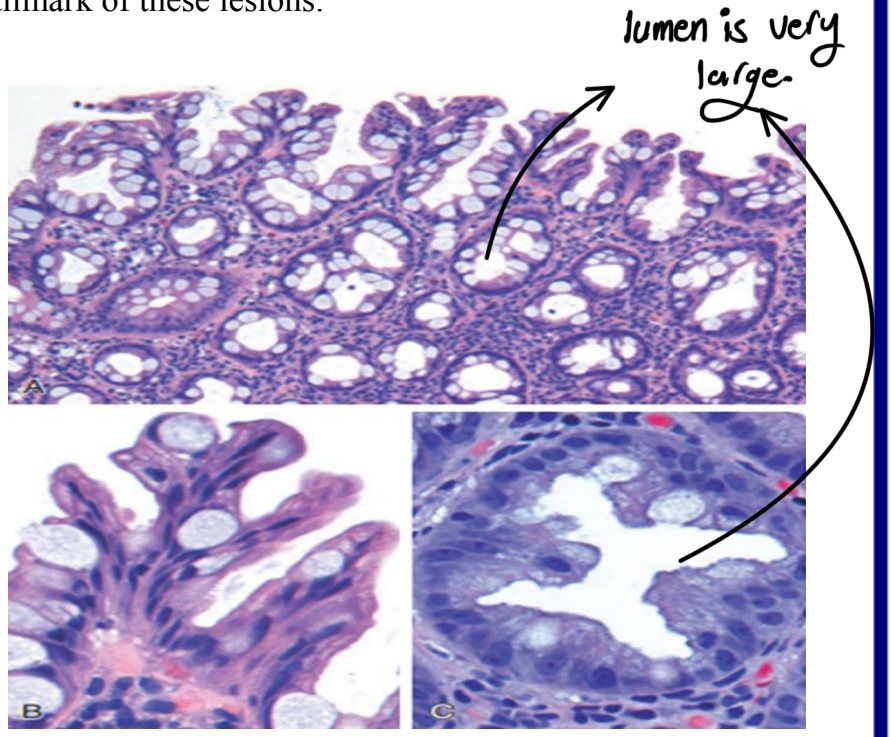
III) HYPERPLASTIC POLYPS (NON-NEOPLASTIC):

- Colonic hyperplastic polyps are very common epithelial proliferations (hyperplasia) that are typically discovered in the fifth to sixth decade of life (old age).
- The formation of these lesions is thought to result from decreased epithelial cell turnover and delayed shedding of surface epithelial cells (i.e. continuous proliferations of intestinal epithelium so that aged cells accumulate forming hyperplastic polyps (long turnover time).
- These lesions have no malignant potential (devoid of dysplasia, totally benign), therefore they must be distinguished from other histologically similar lesions that have malignant potential, as described later.

Epidermal turnover time is the time taken for the epidermis to replace itself.

morphology:

- Hyperplastic polyps are most commonly found in the left colon (specifically; in the recto- sigmoidal area) and typically are less than 5 mm in diameter (small size).
- **Macroscopically**: polyps appear as smooth, nodular protrusions of the mucosa, often on the crests of mucosal folds. They may occur singly but are multiple more frequently.
- **Histologically :** the delayed shedding of epithelial cells (specifically, glandular epithelium) leads to crowding that creates the serrated surface architecture (star-shaped), the morphologic hallmark of these lesions.



macroscopic examination doesn't define the type of the polyps (whether they're inflammatory, hamartomatous, hyperplastic, adenomatous...), that's why the gold standard diagnostic method is the histological examination microscopically.

IV) COLONIC ADENOMAS (NEOPLASTIC):

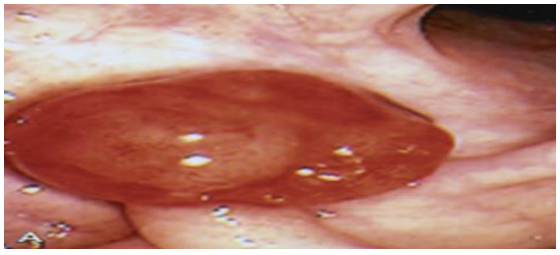
- The **most common and clinically important neoplastic polyps** are colonic adenomas, benign polyps that give rise to a majority of colorectal adenocarcinomas.
- They are characterized by the presence of epithelial dysplasia (low grade or high grade).
- The risk of developing these polyps increases with age and depends on the lifestyle (Western diets and lifestyles increase risk). ← you don't expect to find these polyps in young patients.

- They are precursors to the majority of colorectal adenocarcinomas, so most cases of adenocarcinoma (sporadic and inherited) arise from colonic adenoma.

- Fortunately, most colorectal adenomas behave in a benign fashion (especially in low grade dysplasia) and do not progress to cancer.
- Size of the polyps and grade of dysplasia are important characteristics that correlate with risk for malignancy. **(SIZE is more important).**
- *The larger the size and higher the grade of dysplasia → the higher risk to develop adenocarcinoma.*

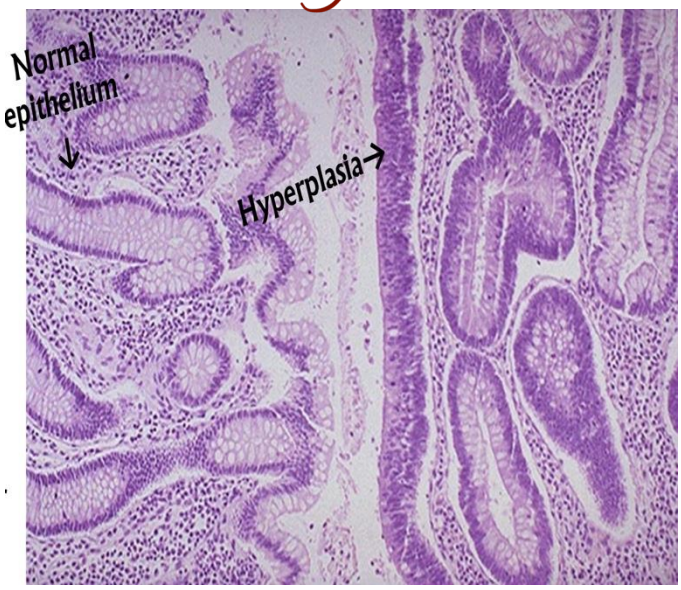
- Current recommendations are that all adults in the United States undergo screening colonoscopy starting at 50 years of age. Additionally, because individuals with a family history are at risk for developing colon cancer earlier in life, they are typically screened at least 10 years before the youngest age at which a relative was diagnosed.

morphology:
- Typical adenomas can be pedunculated or sessile, with the surface of both types having a texture resembling velvet or a raspberry (macroscopically), due to growth pattern.



* Adenoma = dysplasia. (imp. imp.)

- **Histologically** :
(as we said before), the hallmark of colonic adenoma is the presence of epithelial dysplasia which is characterized by **nuclear hyperchromasia** (dark blue nuclei), elongation (cigar-shaped nuclei), and stratification (where in cell nuclei, which are normally located at nearly the same level between adjacent cells, are instead located at different levels)
see the picture .



Adenomas can be classified as **tubular, tubulo-villous, or villous** on the basis of their microscopic architecture .

1) **tubular adenomas tend to be small, rounded or tubular glands.**
2) **villous adenomas, which are often larger and sessile, are covered by slender villi (similar to intestinal villi)**.
3) **Tubulo-villous adenomas have a mixture of tubular and villous elements.**

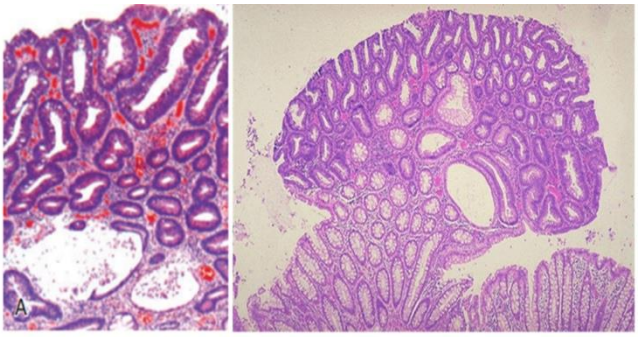
Although the three types are dysplastic and may progress to adenocarcinoma, the foci of invasion are more frequent in villous adenomas than in tubular adenomas.

- Keep in mind that size is **the most important characteristic that correlates with risk for malignancy**

(the 2nd most important factor is the grade of dysplasia).
Therefore, villous architecture alone does not increase cancer risk when polyp size is considered.

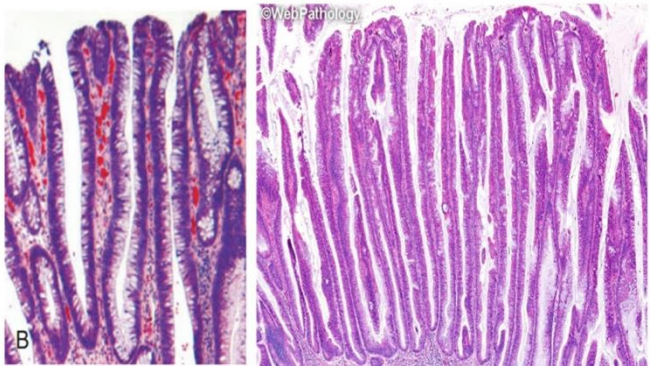
Multiple crypts (glands/tubes) →

Tubular adenoma



Finger-like projections→

Villous adenoma



V) FAMILIAL SYNDROMES

Several inherited syndromes associated with colonic polyps and increased rates of colon cancer. We'll discuss two of these syndromes:

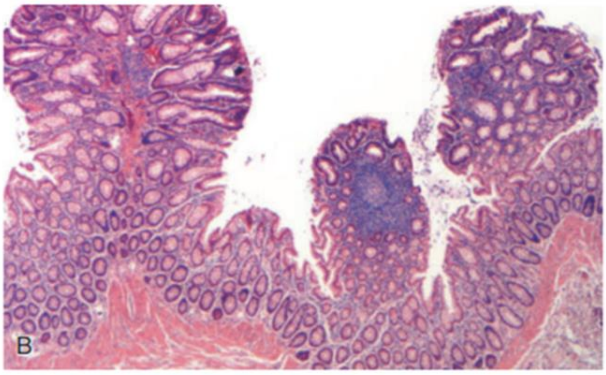
1. **Familial Adenomatous Polyposis (FAP).**
2. **Hereditary non-polyposis colorectal cancer (HNPCC).**

1) Familial Adenomatous Polyposis (FAP):

- It's an autosomal dominant disorder marked by the appearance of numerous colorectal adenomas (not hyperplastic polyps) by the teenage years.
- It is caused by mutations of the adenomatous polyposis coli gene (APC).
- A count of at least 100 polyps is necessary for a diagnosis of "classic FAP". Additionally, these growths are morphologically indistinguishable from sporadic non-inherited adenomas.

Note: sporadic colonic adenomas vary in number from one to a few polyps. On the other hand, FAP polyps are present in hundreds.

- Colorectal adenocarcinoma develops in 100% of patients with untreated FAP often before 30 years of age. As a result, prophylactic colectomy is standard therapy for individuals (<20 y/o) carrying APC mutations. However, patients remain at risk for extraintestinal manifestations, including neoplasia at other sites.



Three (few) tubular adenomas are present in this single microscopic field (note the cysts, that's why it's tubular) ↑

Hundreds of small colonic polyps are present along with a dominant polyp (it's like a carpet covered by multiple polyps, and the intestinal mucosa is lost, the large mass could be adenocarcinoma) ↓

- Specific APC mutations are associated with the development of many manifestations of FAP (other than the "classic FAP") such as "**Gardner syndrome**" and "**Turcot syndrome**".
- In addition to intestinal polyps, clinical features of **Gardner syndrome** (which is a variant of FAP) may include:
  1)osteomas of the mandible, skull, and long bones.
  2) epidermal cysts.
  3) desmoid and thyroid tumors.
  4) dental abnormalities.

الدكتوره حكت انه الجزء بـ Gardner: انها مرتبطة Thyroid بـ tumor:

- Therefore, Gardner syndrome is associated with colorectal adenocarcinoma (due to the presence of intestinal polyps) and thyroid tumors.

Turcot syndrome (which is another variant of FAP) is characterized by intestinal adenomas –too- and tumors of the central nervous system (medulloblastomas >> glioblastomas

الجزء هون: Turcot انه زل بعرفيها: CNS Changes.

3) **Hereditary Non-Polyposis Colorectal Cancer** (HNPCC):

- It's also known as "Lynch syndrome".
- originally was described as familial clustering of cancers at several sites including the colorectum, endometrium, stomach, ovary, ureters ,brain , small bowel, hepato-biliary tract, and skin.

- Colon cancers (e.g. cecal, colorectal) in patients with HNPCC tend to occur at younger ages than sporadic colon cancers and are often located in the right colon.

- Mucin production is usually prominent.

Sporadic colon cancers (colonic adenocarcinoma) usually occur at old ages. Therefore, young patients who have colorectal cancer should test for both FAP and HNPCC syndromes.

- Adenomas are present in HNPCC, but excessive numbers (polyposis) is not.

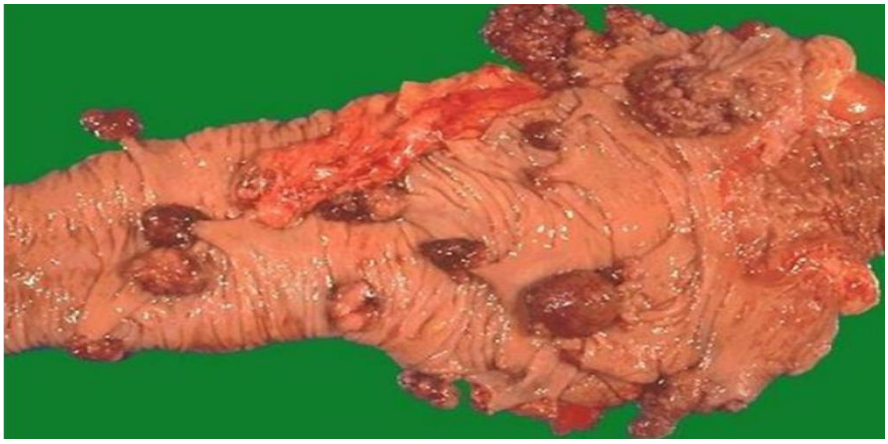
Polyposis → (X)
Polyps → (√)

- HNPCC is caused by inherited germ line mutations in genes that encode proteins responsible for the mismatch repair of errors that occur during DNA replication.

- Defects in mismatch repair lead to the accumulation of mutations, mostly in regions containing short repeating DNA sequences referred to as **micro-satellite** DNA leading to what we call "micro-satellite instability", which leads to further accumulation of numerous mutations across the genome.

- The majority of HNPCC cases involve either **MSH2 or MLH1 microsatellite genes.**

- The picture shows a cut from the right colon, note that there are few polyps, there is no polyposis.



هذا الشيت طويل لأنه عبارة عن
محاضرة ونصف .. وبسهولة يا مؤمن ..

Good Luck ♥