Digestive System

University of Jordan

Faculty of Medicine

Batch of 2013-2019

Medical Committee
The University of Jordan

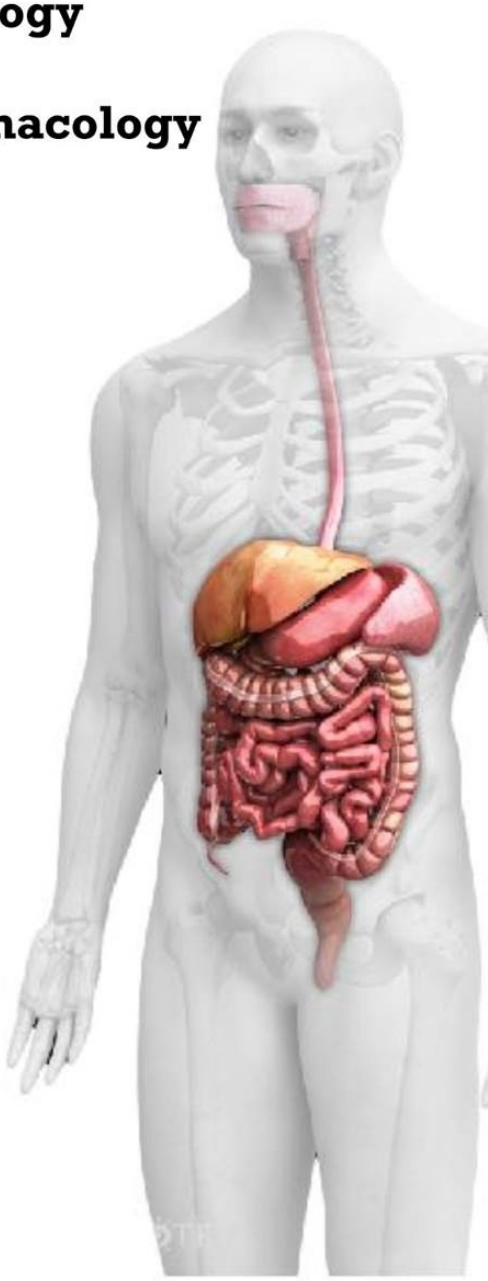
◯ Slide ● Sheet ◯ Handout ◯ Other

☐ Anatomy ☐ Embryology

☐ Physiology ☐ Histology

☒ Pathology ☐ Pharmacology

☐ Microbiology ☐ PBL



Sheet #: 6

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Date:

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DESIGNED BY: TAMER ALTAMIMI "SMILE"

Small and large intestine

Anything written in italic form is from the book.

The slides that need explanation and pointing especially histology ones are included but not all of them are, so I'll have to ask you to check them each time we need them... maybe it's long because of the images but it's really simple and لطيفة :P

Today's lecture is about small and large intestinal NEOPLASIA mainly , mostly the large intestinal neoplasia because they're the **more common**.

Starting with **benign** condition :

1- Intestinal polyps .

**Polyps are most common in colon ,*but may occur in esophagus ,stomach or small intestine*.

**Polyps can either be sessile or pedunculated :
Those **without stalk (you find them on the surface on the colon or intestine)** are called **sessile** .On the other hand ,polyps **with stalks** are called pedunculated.

**As in the stomach ,polyps could be:

1-non-neoplastic:

A)Inflammatory polyps. B) Hamartomatous polyps. C) Hyperplastic polyps

Or 2- neoplastic polyps .

Now to talk about them in separation :

A)inflammatory polyps .

the dr asked us to read it from the book and it's a small paragraph so I copied it here :

" *the polyp that forms as part of the* ***solitary rectal ulcer syndrome*** *is an example of the purely inflammatory lesion. Patients present with the clinical triad of rectal bleeding + mucus discharge+ inflammatory lesion of the anterior rectal wall. The underlying cause is impaired relaxation of the anorectal sphincter ,creating a sharp angle at the anterior rectal shelf .this leads to recurrent abrasion and ulceration of the overlying rectal mucosa .chronic cycles of injury and healing produce a polypoid mass made up of inflamed and reactive mucosal tissue.* "
-Robbins, P592

B)Hamartomatous

It's an abnormal development/organization of tissue which are normally there. So abnormal structures but normal tissue type .

We'll talk about two types :

1-Juvenile

*__Among__ the Hamartomatous polyps ,the **Juvenile polyps** are the most common ,and juvenile literally means **Young** ,so it happens in age < 5 year .

* __Two types__ : sporadic or familial associated (syndromic):

In sporadic or syndromic ,If you look at the polyp itself ,you won't find any difference so ***they are indistinguishable*** .However ,in syndromic ,you'll typically find **multiple** polyps *"from 3-100* " as well as other **problems**. "dr said : there's a nice table in the book of the syndromes that will summarize part of what we are talking about" ,P593.

In syndromic, there is an increased risk of adenocarsinoma ,but in sporadic (which is single) there is not.

Note: In syndromic cases , the **autosomal dominant "juvenile polyposis"** syndrome is the most common.

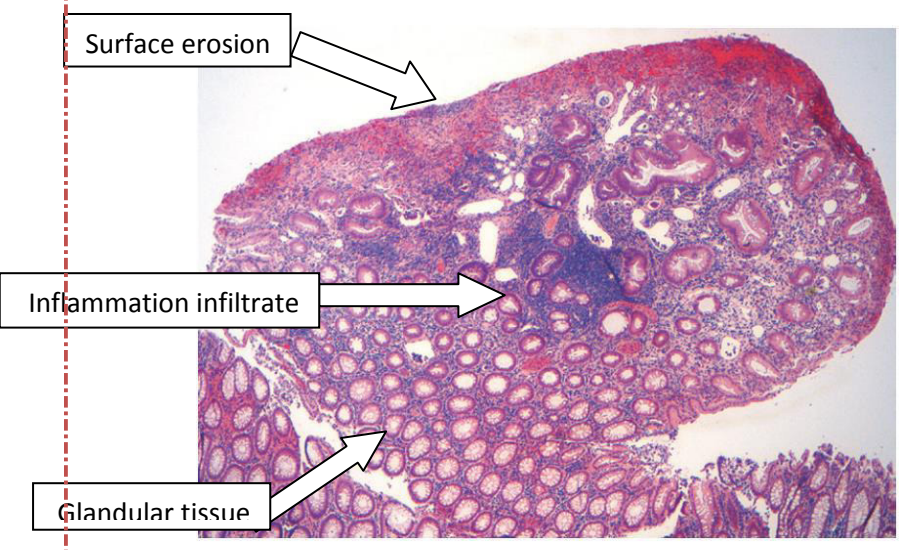
In conclusion : the two types are not different in the polyp itself BUT different in the number and the risk of developing into cancer.

****location** of the juvenile polyps in general: Rectum.

****represent clinically**:

1-bleeding.

2- prolapse "المتدلي":anything that has a stalk or something like it ,such as hemorrhoid or polyp going beyond the anorectal line and present to outside.
book : polyp protrudes through the anal sphincter.



****histology:**
mess of normal cells that should be there but yet not forming the proper structure . you can see the glandular tissue , inflammatory infiltrate "that's why the sporadic may be mistaken as inflammatory polyps when they are actually Hamartomatous polyps."

Other histology features : the polyps are pedunculated, smooth surfaced, reddish lesions ,<3 cm "not a heart :P "
surface erosion , cystically dilated crypts filled with mucus, neutrophils, and debris.

In the syndromic : because you have multiple *"could reach 100"* polyps ,so

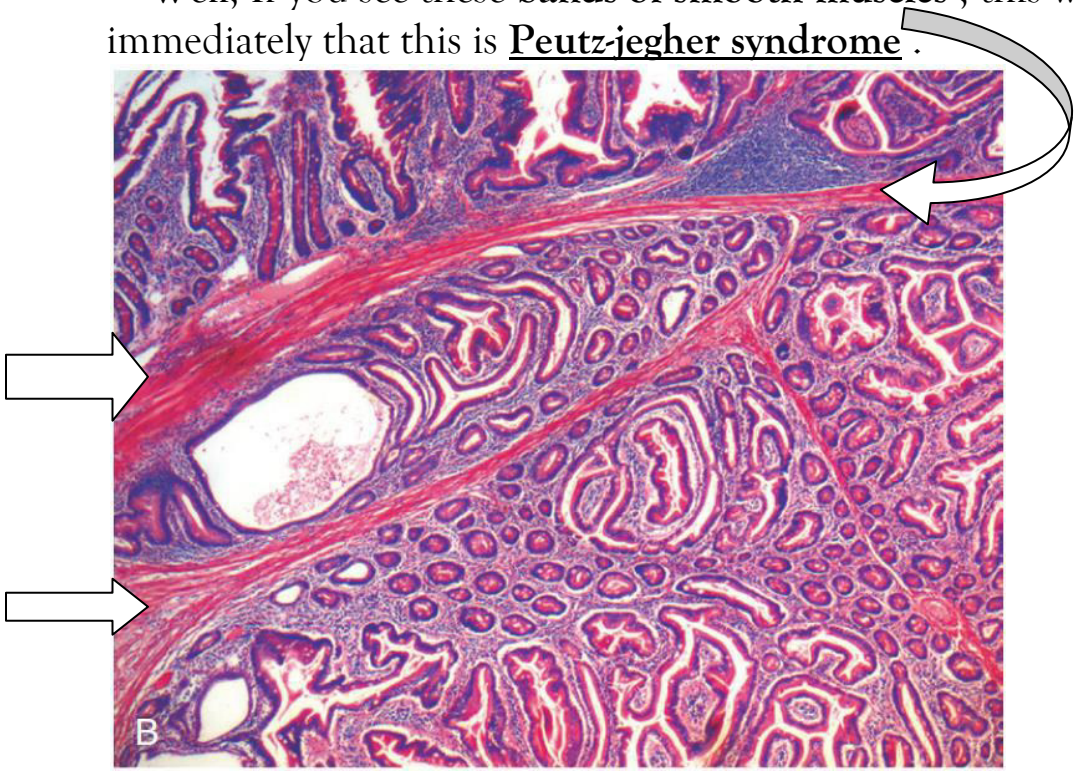
patients present clinically bleeding بغزارة **profusely** from these polyps , sometime colectomy استئصال جزء أو كامل القولون may be required . *It's required to limit the hemorrhage associated with polyp ulceration in juvenile polyposis.*

2-peutz-jeghers syndrome

It's a *rare* Autosomal dominant mutation in *STK11/LKB1 gene* .This gene is responsible for **cell polarity**, so the cells no longer know which way is up and which way is down, and that's why **histologically** they have a **bizarre architecture** . Also you can find glandular tissue.

Now both the Juvenile and the Peutz-jeghers syndromes have glandular feature, so how to differentiate ?

Well, If you see these **bands of smooth muscles** , this will tell you immediately that this is **Peutz-jegher syndrome** .



So histology goes like this :

Large, pedunculated with a lobulated contour with **Complex glandular architecture and bundles of smooth muscle.**

**these polyps are :

-multiple.

-associated with mucocutaneous hyper-pigmentation.

-increased malignancy risk.

-most common in SMALL intestine but also occur else in stomach ,colon, bladder and lungs .

These patients also have increased risk for all sort of unusual tumors all around the body.

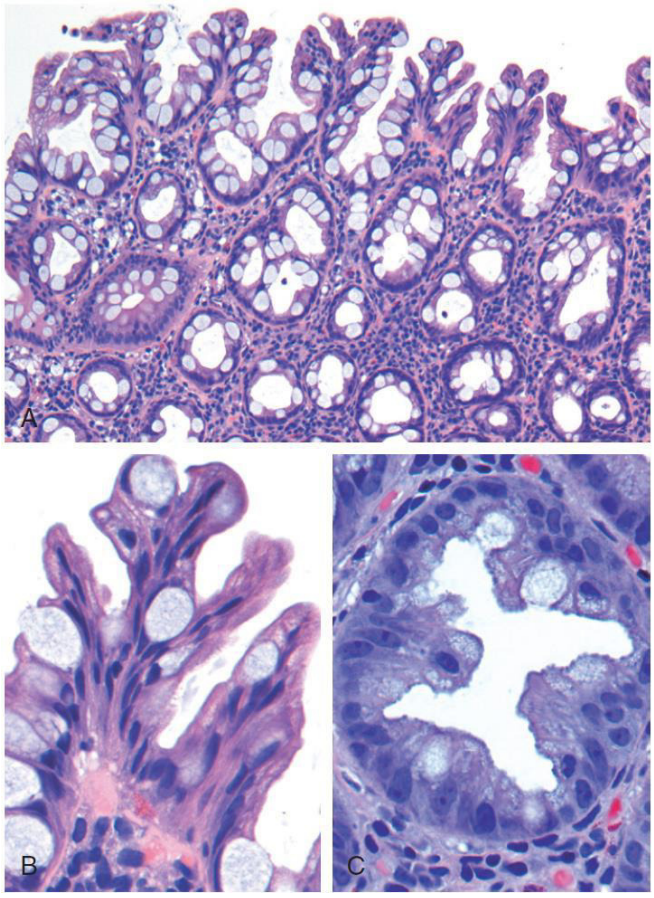
C) Hyperplasia polyps :

-Occur with age 6-7th decades of someone's life

-NO malignant potential , but stay tuned "differential diagnosis " : they look very very similar to a specific type of **sessile adenoma** "we will talk about it later on" which does have a malignant potential . Also note that both of them do have this **serrated appearance** where these **goblet cells** are now punched at the very tops of the crypts ,the serration do not extending all the way to the bottom of the **crypts in hyperplastic polyps , unlike the sessile adenoma in which the serrations extends to the bottom.**

-they are multiple and small < 0.5 cm typically in left colon .

Even though we don't fully understand the pathogenesis ,we think as you age your gut slows down ,you're no longer proliferating gut cells as quickly and no longer shedding as quickly trying to compensate the lack of proliferation , You get these punching of the cells specifically the goblet cells which are really characteristic especially at the tops of folds of intestine.



Smooth, nodular protrusions of the mucosa, often on the crests of mucosal folds

Delayed shedding of mature goblet and absorptive cells creates a serrated surface

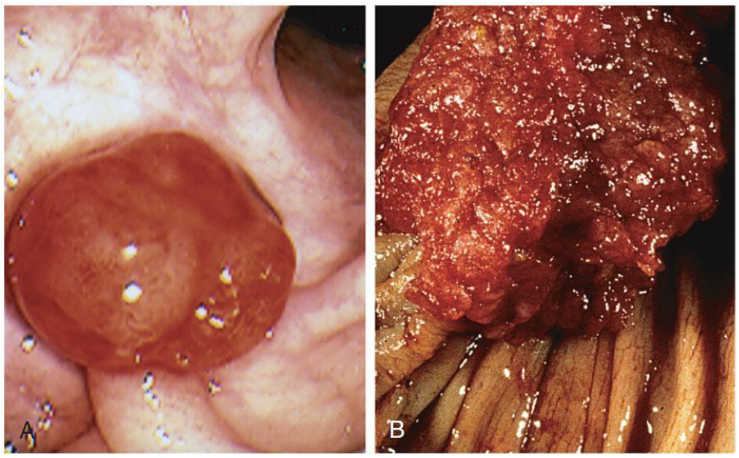
D)neoplastic polyps

-adenoma

Vast majority Of colorectal carcinoma occurs ON TOP or IN adenoma but not all adenomas or even the most of adenoma turn into adenocarcinoma.

Very important -epithelial dysplasia is characteristic of adenoma.

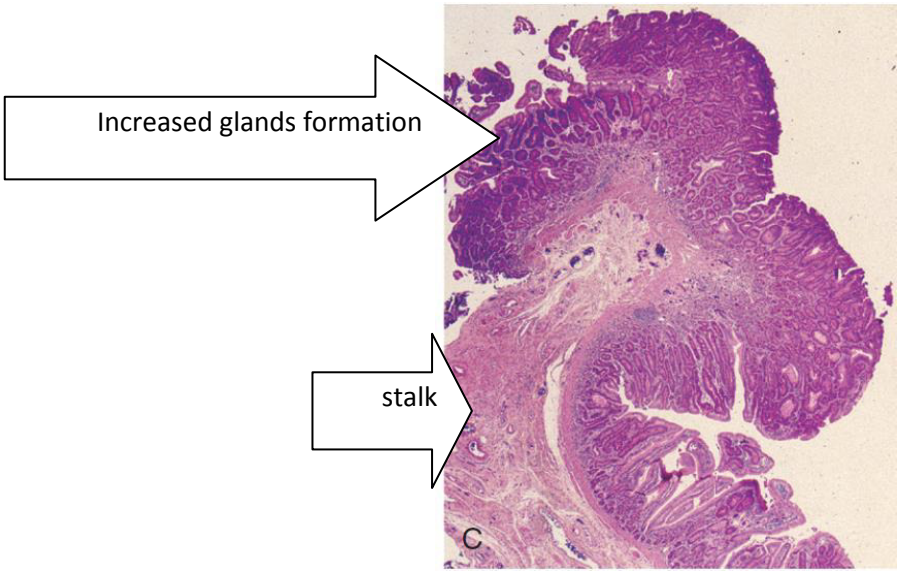
Adenoma polyps can be : pedunculated or sessile



Endosopic

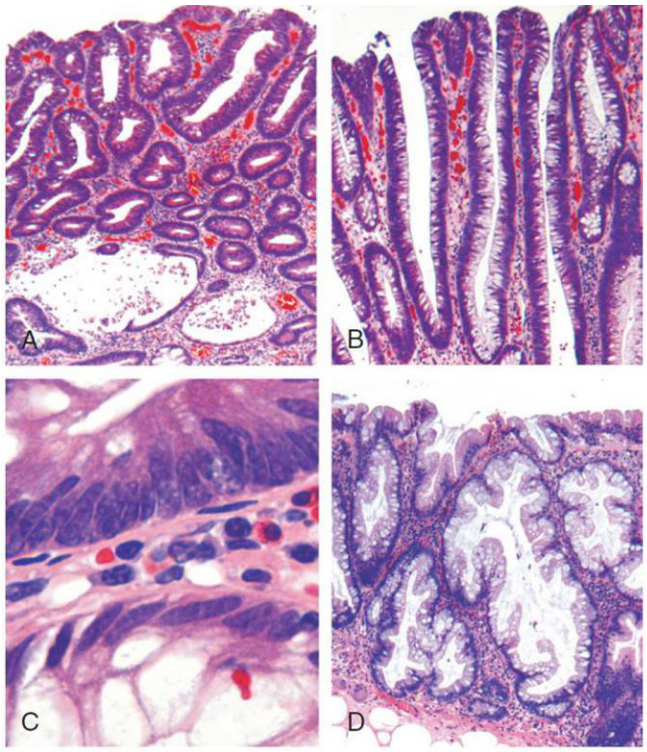
Cut out

surface texture of both types resemble velvet/ raspberry.



*Epithelial dysplasia shown in low-magnification of a **pedunculated** tubular adenoma.*

The polyp here looks as any polyp we have seen before in the previous lecture , but If you look closely under the microscope ,you can differentiate **4 types**:



1. **small tubular**. (image A)
2. **large villous :** long cylinder structure . Remember : villous adenoma is a pre-neoplastic region . (image B)
3. **tubulovillos :** mixed (no image)

note : villous adenoma is more associate with adenocarcinoma than tubular adenoma ,and the only reason for that is because villous are typically larger , SO if you take a villous adenoma and a tubular adenoma of the same size ,they'll have the same malignant potential .

**concerning image C : Epithelial dysplasia :

Nuclear hyperchromasia , elongation , stratification ,"the nuclei are very dark ,elongated and pseudostratified making that mucosa looks as if it has stratified mucosa but in reality it's a single layer mucosa .

4. Sessile serrated adenoma (image D) :

we talked about it .. **differential diagnosis** of hyperplastic polyps ..the difference is the serration that extends all way to the bottom of the crypts in case of sessile serrated adenoma , whereas in hyperplasic it is typically

superficial . Also ,sessile adenomas do occur in right colon but hyperplastic in left colon.

Also Note :

Unlike all 1,2,3 types of adenoma polyps ..the epithelial dysplasia is absent in type 4 (sessile adenoma). **so epithelial dysplasia won't save the day here in differential diagnosis with hyperplasia** but you have to go and look at whole cut out section to tell.

IN conclusion :

Criteria /type	location	Histology : serrated architecture	Malignant potential
hyperplastic	Left colon	Superficial	No
Sessile serrated adenoma	Right colon	Throughout the **full** length of the Crypts.	yes

In general the four types of adenoma depend on the **SIZE "the most important determent " to actually turn into adenocarcinoma or to have a "problem":

< 1 cm unlikely to turn into adenocarcinoma

>4 cm almost half of them will already have adenocarcinoma.

**There are syndromes that are mentioned in the table"book" but here we are to discus two syndromes :

1-FAP

**Familial adenomatous polyps coli syndrome

**It's autosomal domentant and the mutation is in gene APC" adenomatous polyposis coli " the vast majority but the less common is the mutation in gene MUTYH.

Gene APC gives APC protein which is responsible for destruction of B-catenin, so destroying B-catenin and result in stopping B-catenin from inducing proliferation through, example MYC expression ." check the slide"

The other mutations which are less **MUTYH gene mutation** "it's a base excision repair gene ".

Diagnosis :

A count of at least 100 polyps endoscopy "YES , we count them !"

There are **variants of FAP** ,they all have the same colorectal risk but they have intestinal and extra intestinal manifestation like, these variants :

1- Gardner syndrome ..may include Osteomas ,desmoids , skin cysts ,thyroid neoplasia.
2- Turcor syndrome ,is rarer intestinal adenoma associated with CNS tumors ,and here depending on the gene mutated : APC mutation

is associated with medullobelastoma but MUTYH mutation is associated with glioblastoma.

" Checking the slides"

you can see hundreds of small colonic polyps are present along with a one dominant polyp..which type of polyps is this ? tubular type, and you can see **three** tubular adenomatous in this one image.

100% of untreated FAP patients will develop colorectal adenocarcinoma by the **age of 30**! that's why **prophylactic colectomy** is the standard therapy for patients carrying APC mutation. However this therapy won't affect the other extraintestinal manifestation, so your patient **will still be at risk of the these manifestation including Neoplasia at other sites**.

2-hereditary nonpolyposis colorectal cancer/ Lynch syndrome.

Autosomal dominant; like APC, there's an increased risk and always remember you need to lose both alleles for neoplastic transformation.

DNA mismatch repair gene defects mostly **MSH2 or MLH1 , Right** colon predilection and patient present at **younger** ages.
Because it's a DNA mismatch repair, it's not directly related to colorectal cancer ,it produces **Mutator phenotype** (e.g. TGF beta type II receptors, BAX), the first thing you might see is the **Microsatellite instability. why ? because mismatch repair genes are responsible for maintaining your microsatellite which we use in DNA fingerprinting .**

BUT can also affect regions that have microsatellites that are coding like TGF beta receptors and apoptosis genes BAX "apoptosis channels".

Now the malignant polyps:

ADENOCARCINOMA

1-Adenocarcinoma that result from adenoma-carcinoma sequence (APC/Wnt).

**80% of sporadic tumors .

The Mechanism :

Firstly you lose one APC gene: either in a germline "inherited" case as FAP patients OR sporadic "acquired" and that is the FIRST HIT .

Remember :khundson's two-hit hypothesis

Secondly ,The SECOND HIT which can be in **APC** or less frequently **B-catenin** which both are in the same pathway (this step occurs before you even develop adenoma or the polyps)

Thirdly you start producing ADENOMA so now you have more abnormalities like more mutation in "KRAS –proto-oncogene" , p53 ,SMAD2 and SMAD 4, you could have over-expression of COX-2, so you are talking about multiple pathways occurring along the way , TGF beta abnormalities , DNA repair abnormalities and oncogenic activation or RAS that can lead to proliferation .

Eventually you end up with carcinoma and **late** in the disease **Telomerase** ,it's frequently activated in vast majority of these cancers to make sure

that these cells after a while don't stop proliferation but actually continue to proliferate beyond the certain number of cycles that your somatic cells can go through. We are talking about cell senescence vs immortalization of the cell .

"remember the carcinogenesis is a multistep process "

**Most common GIT malignancy is Colon adenocarcinoma .

**Peak incidence 60-70yrs –old people-

**Diet effect :
epidemiologically people who have high fat ,poor fibers are in a higher risk .

****NSAID :**
People who are on chronic low dose aspirin seem to be protected from polyps and colon adenocarcinoma, and this is reflected in the fact that COX2 is overexpressed in 90% of these adenocarcinomas , and what do NSAID do ? They inhibit he COX enzymes which produce certain prostaglandins like PGE2 that can activate oncogenic pathway that increase proliferation.

2- Adenocarcinoma that result from microsatalite instability pathway .

Rather than APC mutation you have mismatch repair gene mutation that leads to abnormalities in mismatch repair, microsatalite instability (TGF beta 2 receptors ,BAX , BRAF ,TCF-4 , IGF2R)=mutator phenotype, you are going to get all sources of mutation, you can also end up with carcinoma.
What is unique? you won't find KRAS or P53 mutations, because they are in a region where microsatellite stability is not important but there are

plenty of other genes that mimic their function or take over it that are mutated because of the abnormalities in this pathway ."check slides"

Morphology

If you talk about:

1-Proximal colon: the tumors will grow into the lumen and on one side (polypoid, exophytic)

2-Distal colon : the lesions will be annular "napkin ring" الحلقة التي توضع حول المنديل في المطاعم

In the image it's a distal colon lesion (check slides please) .. it's been cut longitudinally ,you can see the thickening on the wall on both sides (arrow) so it's all one circle ((napkin ring constriction)) before and after the ring,you can see a diversion of mucosa but in the middle a constriction and more likely it becomes obstruction .

Both of them grow into the bowel wall and induce desmoplastic reaction which means that they could become palpable in abdominal examination as firm masses .

Also they differ clinically we 'll talk about it at the end .

Now **histology: "check the slides please"

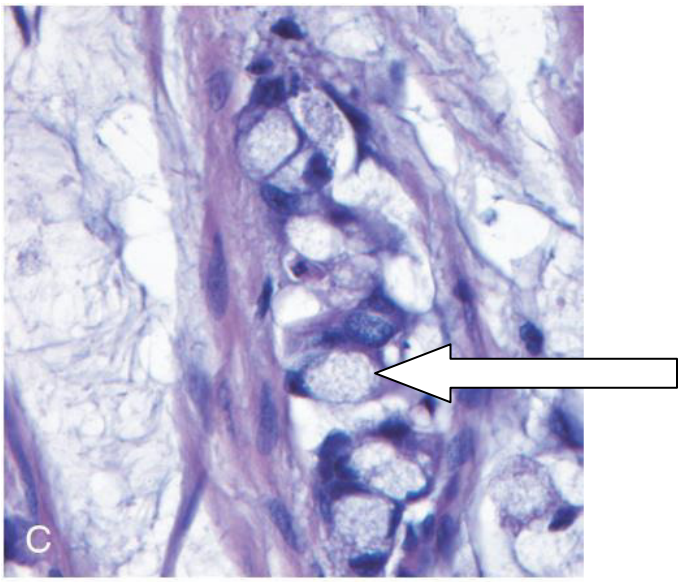
It could be **well** differentiated adenocarcinoma, tall columnar cells with hyperchromatic nuclei resemble epithelial dysplasia also you can see some glandular structure but you find in the lumen of the glands some inflammatory cells, cellular debris.

Or

Poorly differentiated adenocarcinoma: few glands and infiltrating tumor cells

**Clinical history "where the sample came from ,symptoms and age of the patient " is very important to be known before looking at samples .

Look at this sample ,you'll find signet cells -which are present also in the diffused type of gastric cancer – producing lots of mucin.**These patients have a very bad prognosis (aggressive caner).



Clinically :

**In distal lesion "left-sided colorectal" ,patient are more likely to present with obstruction ,bowel habits , cramping , bleeding that could be detected in fecoral blood test.
But Proximal lesions "right-sided colorectal ", patients are more likely to present with fatigue, weekness and tirdness due to iron deficiency anemia SO if the patient is elderly or postmenopausal female with this anemia, it's a gastrointestinal caner until proven otherwise .

**right and left sided large intestine ..anatomically speaking . **

Prognosis

it does depend somehow on the morphology of the cancer but the most important factors are :

1-depth of invasion 2- lymph node metastasis

**Looking at image A "check slides please"

If I tell you this is LN and You can see glandular structures within the subcapsular sinus>> immediately you think of lymph node metastasis of adenocarcinoma .

**Looking at image B
if I tell you this is lung , *you can see solitary subpleural nodule of colorectal carcinoma metastasis*.

**Finally image C: LIVER

You can *see two large and multiple small metastases "yellow things"* .

Most common metastatic site except for rectal cancer !! why ?
well, because you have first past effect in liver portal circulation coming from the colon but in rectum there is portosystemic anastamos, so it will bypass the liver going to lung or bone .

GRADING AND STAGING

I do expect you to memorize for example that T3 invades through the muscularis propria but T2 invades into but not through the muscularis propria.

I also do expect you to recognize that increased in depth of invasion (Tis-T4) and more lymph nodes (Nx-N2) and distant metastasis (mx-m1) have a markedly decreased survival rate .. so be attention to the stage and what that stage means.

Dedication to mai ziad ,farah bilal ,bayan kilani, sally zidan,nadejda baklizi and alia arman

انا بعتذر عن الشيت الطويلة و ادعوا لنا بالخير ☺☺