

6th Lecture

17.10.2021

Pathology - GIT

Polyps

Polyp → ~~bejss~~ ~~cap~~ → not something specific
any thing that does blugh in a hollow organ (تنقبات)
is called polyp, but what's inside it is different.

↳ So it a macroscopic appearance that can be:

- 1 neoplastic
- 2 reactive
- 3 inflammatory
- 4 cancer, or not cancer

We saw ^{in stomach} different types of polyps, and that there were
different types (hyperplastic, hamatomatous (fundic gland polyp)
adenoma)

→ In digestive system the most common area for polyps:
colorectal area.

⇒ Polyps can have different shapes: neoplastic or non neoplastic

1 neoplastic: We're talking about tumor, whether benign or
malignant. We're talking also about a disease / molecular
morphological changes that have some characteristics:
- lost control about cell → leading to mitotic activity
without regulations

2 non neoplastic =

we're talking about something reactive; a reaction against something, that can be **hyperplastic**
حدث معين أدى لأنه الخلية تتراكم ويزيد عددها ويكون كتلة معينة التي تفرج
ال bulging هذا.

Or it can be **hamartoma (hamatomatous)**

multiple ^(normal) tissues that are disorganized that cause polyp
يعني عن الأنسجة الطبيعية كلها موجودة لكن بدون الترتيب المعتاد

common example: Lung hamartoma

Mass in lung (epithelial tissue)

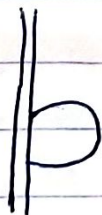
بنوع (فحص) ال mass هادي بنوعها ومكونة من epithelial بنوع
ال epithelium نوع ال RS ، بنوع cartilage و muscle tissue. يعني انهم
اللي يكون ال Lung ال RS لكن بين التنظيم المعتاد

another example: Liver hamartoma

all hepatocytes, colangyocytes, Kupfer cells, blood vessels, keto cell
are present, but not organized

⇒ There are also:

Sessile polyps: relation to wall is broad based
قاس على الجدار قاعدة عريضة



من علم النبات لأنه تفرج في الدفك طالع حاشية

↳ in some cases, size increases

Pedunculated

الآن الـ sessile polyp يبدأ يزيد الحجم، حجم الكتلة يزيد، فعندئذ أنا
أنا ألاحظه - في الـ colon والـ digestive system في سرير مركبة أو
muscle contraction في اتجاه معين، يعمل نوع من الـ traction effect فبدأ
قوة تنسحب في الاتجاه هذا، بالاقتران الـ normal cell فيه
فيها proliferation بعد لها فرغوا (stank)



this is when it's called pedunculated

That all was just a description to its shape, but
the most important is what's inside the polyp.

Sometimes there are some relations:

adenomatous sessile is ^{أكثر} more to have dysplastic
changes, but anyhow at the end - as said - the
inside is important

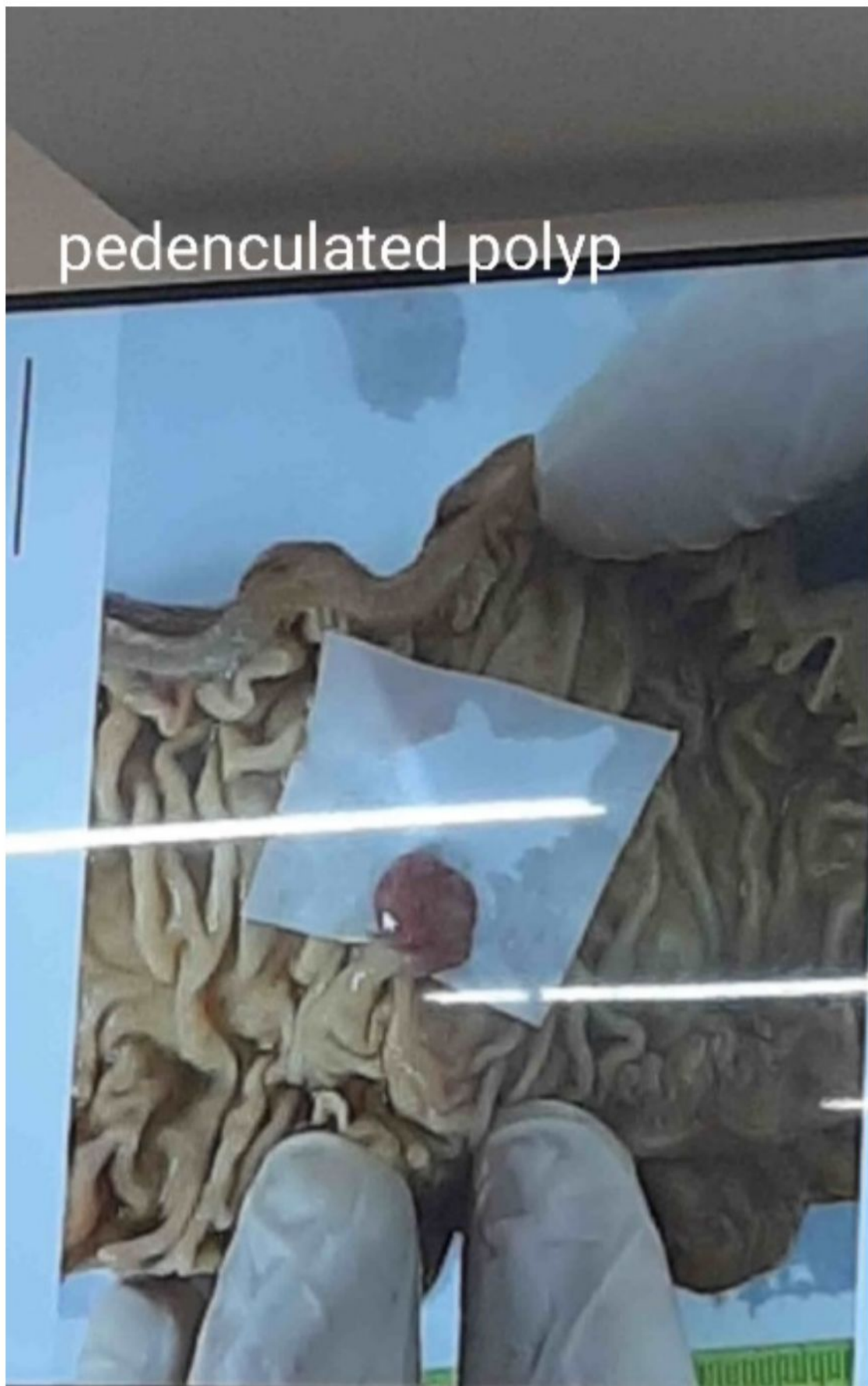
So, that about polyps in general

There are 3 essential types of polyps in the colon

① Hyperplastic Polyp

- As the word says "Hyper" → increase in ^(تعدد) number (hyperplasia)
- usually in elderly
- In sigmoid and rectum most commonly
- Can be single or multiple

pedunculated polyp



Sessile polyp

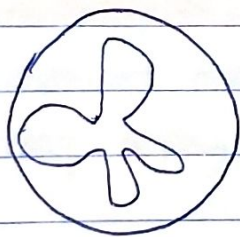


Usually less than one or two cm

Pathogenesis:

لعمريه من hyperplasia بعد ما هو delay في shedding
لا mature cells في خاكرين في crypt فيلنا في عيا
stem cell الي هي مصدر الكاثر وبتنار في مية
Maturation $\rightarrow$ sluffing $\rightarrow$ a new cell degenerates

بمعة ان العمر هنا متعرج متعرج، وتطول هذه المدة لسبب
ما ويصل يصل shedding لكن سرعة، proliferation زي خا
هي مستمرة والتالي هو ميعر في balance يصل في انو
الخلايا تتراكم. لما تتراكم هنا للالا يصل شكل معين بايدينا
في التسمية protrusion towards lumen



Surface epithelium as "star"
 $\rightarrow$ hyperplastic polyp

* Hyperplastic polyps in colon has no potential of malignancy, totally benign. (Remember that in stomach it's different, 1:20 to become malignant)

② Inflammatory Polyp

- Non neoplastic (but in ^{Pre malignant} syndromic case → cancer)
- Tissue or cell injury → repair (mitosis of cells to replace old ones)
→ inflammatory granulation tissue which is proliferation of blood vessels → process continues leading to inflammatory polyp (mass)

"Inflammatory polyp = Granulation tissue"

Pseudo polyp
Hyperplastic, Adenomatous, etc.

Examples:

Solitary rectal ulcer/prolapse

③ Hamartomatous polyps

As mentioned, they are a sum of tissues that are disorganized building a polyp.

- They can be

Sporadic → حالة فردية
(germline mutation) (80%)

a part of syndrome / familial (10-20%)

- Developmental abnormality
- Many of the syndrome reveals germline mutations

- Some syndromes are associated with increased risk of cancer (pre-malignant)

"Genetic defect"

نفاذ على قراب واحة اصاب
منه من cancer في حالة تامة

characteristic for hereditary neoplastic diseases

Syndrome	Mean Age at Presentation (years)	Mutated Genes; Pathway	GI Lesions	Selected Extra-GI Manifestations
Juvenile polyposis	<5	SMAD4, BMPRII, TGF- β signaling pathway	Juvenile polyps; risk of gastric, small intestinal, colonic, and pancreatic adenocarcinoma	Congenital malformations, digital clubbing

Juvenile Polyps

- most cases in children < 5 years (Epidemiology)
- Clinically has different shapes, the most frequent clinical sign: rectal bleeding.

Sporadic juvenile polyp: you can see 1 polyp

"Juvenile polyposis" = "متلازمة في سن مبكرة"

- Autosomal dominant
- from 3-100 polyps
- may be associated with other congenital malformations

Morphologically (as said):

normal tissue but disorganized
(epithelium, mucus secreting goblet cells, dilated glands, inflammatory cells mixed together)

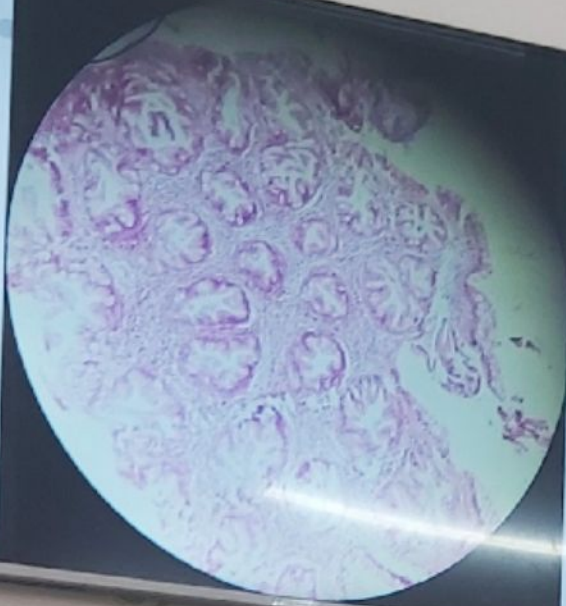
↳ If it reaches a big size → ulceration of surface & dense inflammatory process

Juvenile polyps can be -as said- part of syndrome (Juvenile polyposis) are explained as having mutation

(الطريق الجزيئي) TGF- β → normally does inhibition of proliferation (tumor suppressive gene)
↓

SMAD 4

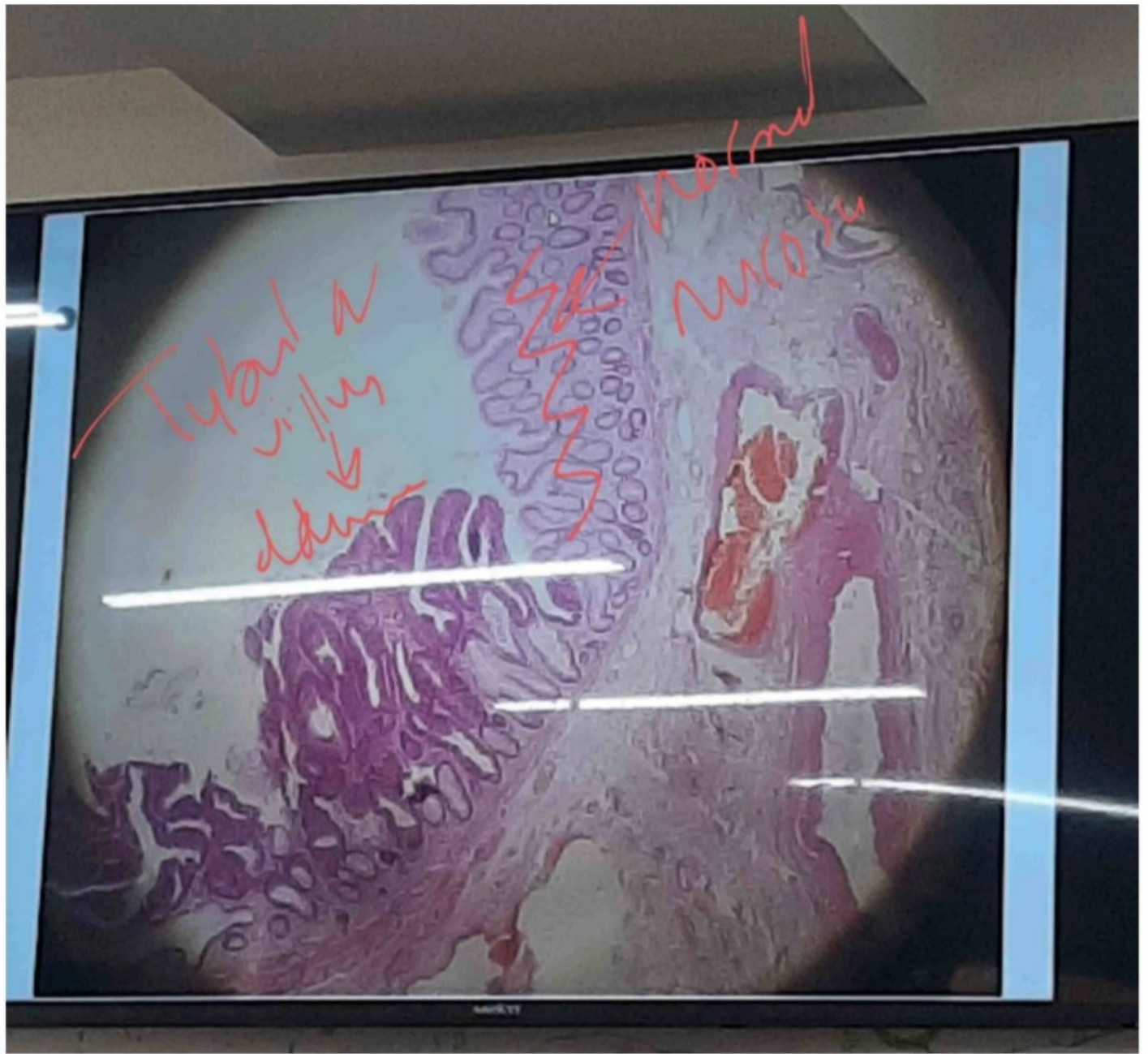
serrated adenoma



Juvenile

Petz-Jeghers





- Dysplasia : - rare in sporadic
- associated with JP
- 30-50% of JP develop adenocarcinoma by age 45

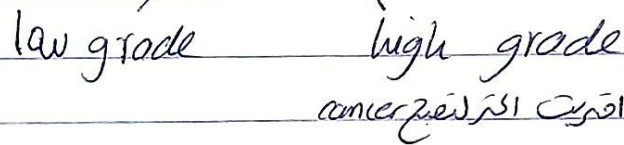
Neoplastic polyps:

Table 17.10 Common Patterns of Sporadic and Familial Colorectal Neoplasia

Etiology	Molecular Defect	Target Genes	Transmission	Predominant Site	Histology
Familial adenomatous polyposis	APC/WNT pathway	APC	Autosomal dominant	None	Tubular, villous; typical adenocarcinoma
MYH-associated polyposis	DNA mismatch repair	MYH	Autosomal recessive	None	Sessile serrated adenoma; mucinous adenocarcinoma
Hereditary non-polyposis colorectal cancer	DNA mismatch repair	MSH2, MLH1	Autosomal dominant	Right side	Sessile serrated adenoma; mucinous adenocarcinoma
Sporadic colon cancer (70%-80%)	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
Sporadic colon cancer (5%-10%)	Hypermethylation	MLH1, BRAF	None	Right side	Sessile serrated adenoma; mucinous adenocarcinoma

Adenoma (استسقاء)

Adenoma = dysplastic changes (pleomorphism, hyperchromasia, nuclear enlargement)



- Adenomas are the precursor of the majority of colorectal adenocarcinoma (adenoma-carcinoma sequence)

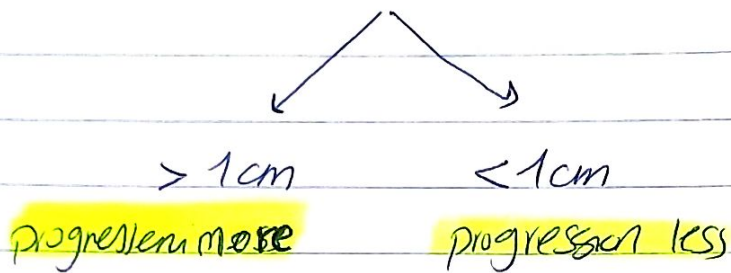
Macroscopically:

can be sessile or pedunculated

Microscopically:

- Can be composed of tubular structures (tubular adenoma).
- Can be composed of villus structures (villus adenoma).
- Can be a mix of both: villus + tubule → Tubulovillus

- Variety of dysplasia ^{& size} is the important (not shape) and also the size



- Surface is sometime smooth or vilvudly

* Not all adenomas have to be cancerous, but all cancers have the adenoma previously before it)

* Colon cancer 3rd most common frequent

* Adenomas usually in 30% by age 60 in west

* less common in Asia

* Surveillance and regular endoscopic examination

espically in areas with high prevalence is very important

↳ and here famular history is helpful

في اجزاء Colon c. على عمر 45 - 50 في اسبانيا و الفرجان (35) ابن
الذي لا يتم فيها اعادة سلف في colonoscopy بشكل منتظم

- The majority don't progress to adenocarcinoma

Clinically:

If small size → not easy to have symptoms
If large → erosion & ulceration → bleeding



Anemia: iron deficiency anemia

Male & postmenopausal who have iron deficiency

→ CRC → is first thought! → CR endoscopic examination

there's a type of adenoma called:

Serrated adenoma

different from tubular, villus & tubulovillous by having potential of malignancy but no ^{visible} dysplastic changes

- ⇒ Hyperplastic polyp: only upper surface & upper part of crypt
- ⇒ Serrated adenoma: crowding of epithelial cells

Remember the normal layers in histology? Muscularis Mucosae, Submucosa, & Muscle layer, Serosa

* Invasion or interruption of basal lamina → Intramucosal carcinoma

⇒ it's importance in CRC? In colon there's no lymphatic in mucosa (lymphatic start at submucosa).

↑
feces

اذى طلقا انه ما غنى / عمل Muscularis Mucosa rupture
 صنف ال carcinoma على ال intramucosal carcinoma
 ف ما سأل من رسل aggressive في تاتل اكر
 على ال muscularis mucosa

At the point where dysplastic changes cross the basal lamina $\rightarrow$ **Invasive Carcinoma**, but if in muscularis mucosa $\rightarrow$ **Intramucosal**, (if at the first layer $\rightarrow$ adenocarcinoma)

As said in first lecture (see 1st Patho) the most important are the stages of a cancer.

T → Tumor size (in CC to which layer it reached)
SM → T₁, MM → T₂, Serosa → T₃, ^{all layers} Out → T₄

N → Lymphoid metastasis

M → Distant Metastasis (أصل إلى أماكن بعيدة)

If there's increase in size ^{of adenoma} → there's more increase in building comu why? Because the size shows that there has passed more time. Because also from molecular view → mutations are more likely to happen in an adenoma with a larger size, and to transform into a cancer cell.

FAP				angiomyolipoma
Classic FAP	10-15	APC	Multiple adenomas	Congenital RPE hypertrophy
Attenuated FAP	40-50	APC	Multiple adenomas	

Familial adenomatous polyposis (FAP)

Adenoma → sporadic, single or few, multiple

- But in some cases and people who carry germline mutations → building of a high number of adenomas (hundreds or thousands)

- * The most important event here (on molecular level) is Mutation of **APC gene**, that works on β -cadherine

β cadherine actually binds to ^{ubiquitin} complex that goes to proteasome where it will be degraded

Let's remember the pathways (**WNT pathway**)
 fundic poly + gastric adenocarcinoma مرض في

→ The GF has on its surface a receptor to which the WNT binds leading to a (once) action:

التي تأتي من الزفير، يبرز signal التي تكون حالة على APC
 يتخلل في β -cadherin. هذا يمنع الطي، وطبقاً للتيه التفاعلية أنه
 ال β -cadherine من صيد على ال nucleus وتكون مع
 انتقام وهذا يمنع الطي لكن فرضاً أنه هذه التي لازمني ننفس
 كما أن مرة أو مرتين في بيت + (أرق)، ال WNT يرتبط بال (receptor)
 وبأدي إلى إعاقة عمل ال APC مؤقتاً، إعاقة عمل ال APC تؤدي
 إلى ال β -cadherine بتركز (accumulation) وترتفع **Translocation**
 على ال nucleus هناك TCF - ال DNA binding factor trigger

Transcription factors لادي لتكوين كاسومون من ال **cyclin** **APC**
اللي حكاهاهم لانه بيقول ال cell cycle، خالي الالة ترتبط مع
ال **cyclin dependent kinase** وبقوله بحيث الالة تنقل من وضع الكون إلى
ال **S-phase**، بجرن الالة في ال **G1**، فالكرين ؟ :

هذا خط سير الامتحان، انقست الالة ← حلس ← نه لمة ودية.

In case a mutation in APC, a mutation that leads to the stop of APC gene, a continuous defect, not for once or under tight control.

→ Cell will work as if it gets continuously a WNT signal without stop → cell will divide without stop

And this type of defect is found in familial cases (FAP)

⇒ Total colectomy (because we have 1000s of polyps)

* **MUTYH** Base excision repair gene, base detection & repair

→ repair DNA إصلاح الالة بوضع

- have less than 100 polyp
- Known for having sessile serrated adenoma

* Most of CC cases go back to APC pathway (FAP) and/or Lynch syndrome (Mismatch)

colon cancer is mostly sporadic, the Familial cases make up a minority, (and we said that familial cases are dangerous also for their relatives).

From studying the familial cases APC, WNT pathway, mismatch repair pathway we came to that the events happening in familial cases are the same happening in sporadic ones, but the difference is that familial is germline hereditary for mutation, but sporadic are somatic (not found in all cells of patient)

#NPCC (Lynch syndrome)

- Hereditary non-polyposis colorectal carcinoma
- What happens is a mismatch deficiency, that goes back to DNA-repair
- 2-4% from all colon cancer cases but also the most common syndromic form
- in younger age than sporadic cases
- usually in right colon

Microscopically:

- type of cancer is called mucinous type
- around tumor are many lymphocytes → lymphocytic infiltration

و infiltration of lymphocytes dense ، يعني لو شافنا خلية طحينة في الـ mismatch ← HNPCC ← في الخلية التي في القولون

فالتالي عتد نعد، نفسى فترابى بره وفضل يتابعه
لانه وارد على صحت بي كمان فى مناطق اخرى.

* FAP and lynch syndrome were the base in understanding sporadic cases, with difference that they happen in germline mutation (FAP & HNPCC) but sporadic are somatic mutations

Mismatch repair:

لا تقول حصة المس مانتش ...

There are a sum of genes that have a relation to this and do DNA repair. So these genes do in some way a scanning for this DNA, before it enters the new mitosis. (P53 has also a relation)

so if the repair went well → نفسى المس، نفسى المس
if not → should be referred to apoptosis

MLH1, MSH2, MSH6, PMS2 are these genes

نفسى علاج الفرق موشى على

The majority of patients: MSH2, MLH1

* usually inheritance happens and the mutation goes from generation to generation, they are recessive (on second allele)
"السرى يكون فرعى"

* Accumulation of mutations 1000x higher than normal.

الموتة الثانية في طوفان mismatch

Those genes make a defect → mutations, so these mutations related to mismatch repair prefer special places on the DNA, called **microsatellite** which are short repeating sequences ≈ 100 on the DNA. (100,000-500,000 sequence) Those microsatellites are also close to important parts related to carcinogenesis.

Lots of mutations on microsatellite → **microsatellite instability**
MSI

*MMR, MSI, Lynch syndrome, HNPCC → **حكم على كافة درجة**
ولكم نفس القدر

*WNT, APC, β -catenin, TCF, MIC cycline → **كلوا عن طريق درجة**

Epidemiologically, CC 3rd place

Colon → 1,20 - 1,50 cm

SI → 5-6 m → frequency of tumors less even though it's larger

- 10% worldwide of cancer mortality go back to CC
- Yearly, there are ~~to~~ 1.5 million new cases of CC

→ half of the die

- highest incidence in ^{2nd} USA, fat rich diet plays a role while vegetables and fiber ~~rich~~ are important → problem in digestive system (Hamburg, ...)

- low incidence in Africa & parts of Asia
- 60-70 age but often also younger

NSAIDs inhibits possibility of getting CC, because it inhibits cyclooxygenase 2 which produces Prostaglandin E_2 that has a mitogenic effect $\rightarrow$ inhibition of growth

Summary of Pathogenesis

- ^{bases in the} **genetically** $\rightarrow$ from familial cases, MM, MSI, LS APC
 $\rightarrow$ in sporadic same but somatic
- **Epigenetic** $\rightarrow$ histone or something outside nucleotides
as = methylation induced silencing
there's no problem in gene but hypermethylation $\rightarrow$ no expression of gene $\rightarrow$ important in tumor suppressive genes

APC / β -Catenin pathway (again)

- The classic adenoma carcinoma sequence
- 80% of sporadic cases
- happens usually in young age (adenoma stage even)
- **mutation** can happen in **β -Catenin** and reaching to not binding to APC $\rightarrow$ same result $\rightarrow$ $\uparrow$ F1r
- **Oncogene** $\rightarrow$ $\uparrow$ proliferation cells $\rightarrow$ $\uparrow$ mitosis & onco vi cells
Tumor suppressive $\rightarrow$ keeping cell

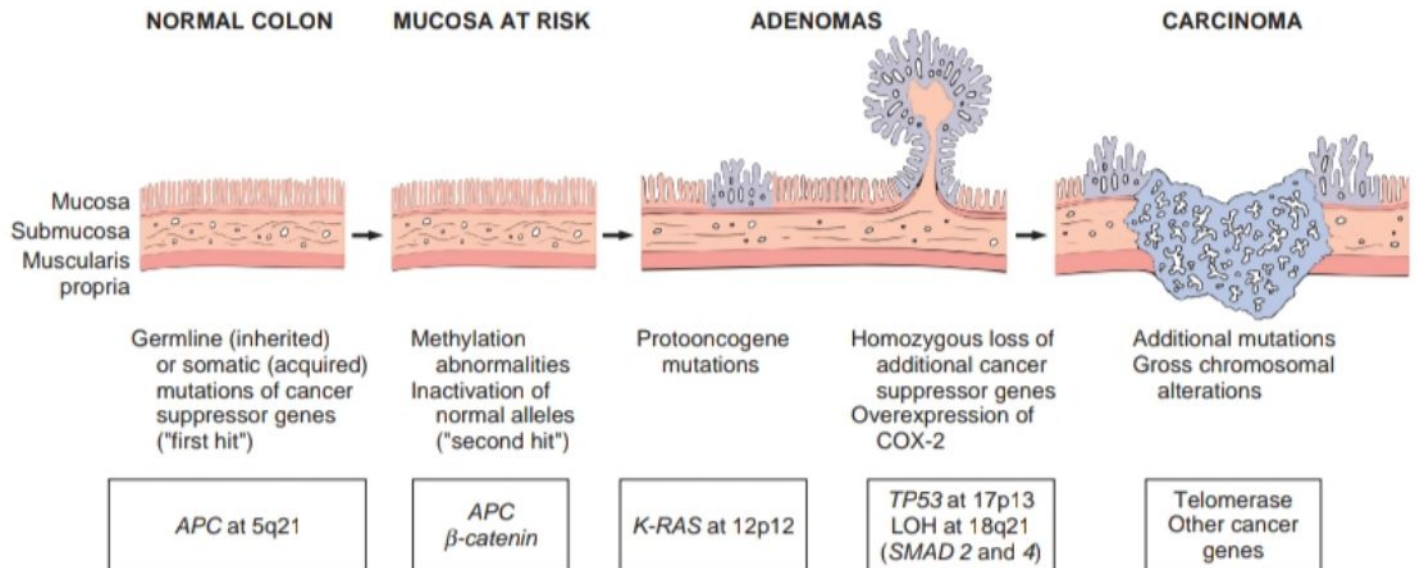


Figure 17.49 Morphologic and molecular changes in the adenoma-carcinoma sequence. Loss of one normal copy of the tumor suppressor gene *APC* occurs early. Individuals born with one mutant allele are therefore at increased risk of developing colon cancer. Alternatively, inactivation of *APC* in colonic epithelium may occur later in life. This is the "first hit" according to the Knudson hypothesis (Chapter 7). The loss of the intact second copy of *APC* follows ("second hit"). Other changes, including mutation of *KRAS*, losses at 18q21 involving *SMAD2* and *SMAD4*, and inactivation of the tumor suppressor gene *TP53*, lead to the emergence of carcinoma. Although there seems to be a temporal sequence of changes, the accumulation of mutations, rather than their occurrence in a specific order, is most critical.

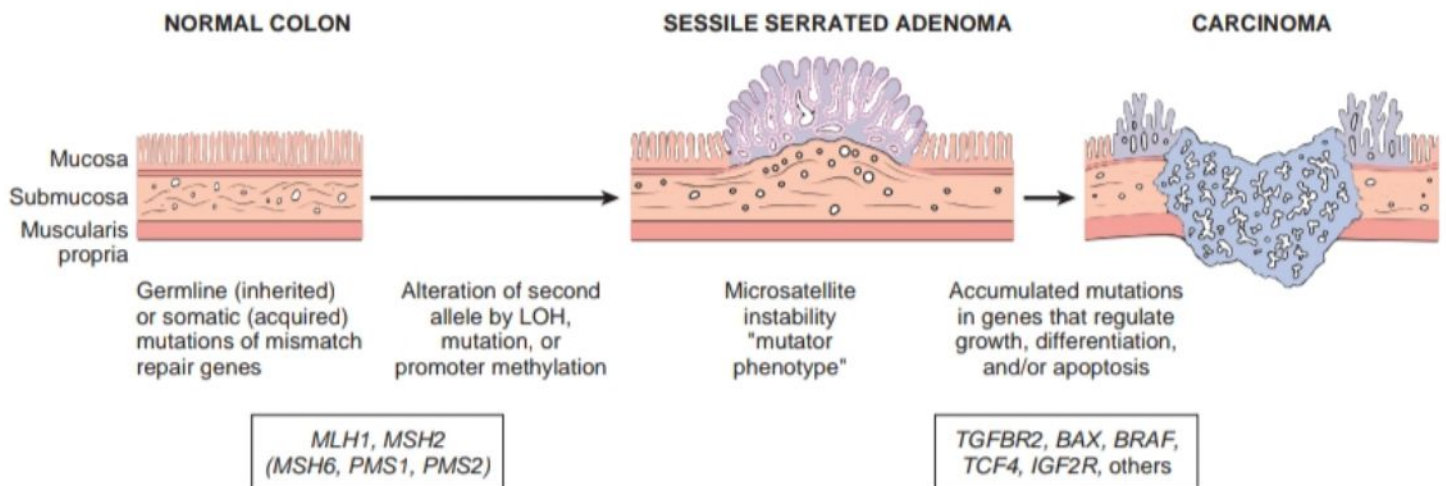


Figure 17.50 Morphologic and molecular changes in the mismatch repair pathway of colon carcinogenesis. Defects in mismatch repair genes result in microsatellite instability and permit accumulation of mutations in numerous genes. If these mutations affect genes involved in cell survival and proliferation, cancer may develop.

APC & MSI (الوراثي)

Additional mutations

as KRAS: a transduction protein that has different categories, if activated by epidermal growth factor with receptor will activate transduction mechanism (KRAS)

↳ ~~can~~ mutated & frequently

⇒ promote growth → Protooncogene normally but when mutated oncogene

→ on another side it works on stopping apoptosis

⇒ Addition to first part of lecture:

in 10% from the adenomas less than 1 cm are KRAS mutations seen, and 50% of big ^{adeno} adenocarcinomas have KRAS mutation → so, happens at the late stages of adenocarcinoma

So to summarize:

- Promote growth
- Prevent apoptosis
- Fewer than 10% of adenomas less than 1 cm
- 50% of adenocarcinomas larger than 1 cm
- In 50% of adenocarcinoma
- Late mutation in cancer

Transforming growth factor B (found nearly everywhere)

which is inhibitor for proliferation → has SMAD group inside which are tumor suppressor genes, so their loss would mean mutation

And **TP53** (the guardian of the genome)
- not common in Adenoma → found in late stages

Telomere

↳ the last part of telomere is repeated sequences
- non coding, short repeated sequences

لما يصل انتقام، الانتقام يبدأ في النهاية لتفقد من أجزاء
أو نسخة خلية، فافيا هناك نقل coding وانما هي لاجل
مكتوبة في كل انتقام بنوع جزي (chromosome) وهذا من حالة
مفهوم الخلايا في جسم الانسان لو كان عدد من الانتقامات
وبعد ما يتفقد في الشيخوخة ونتم ال cell death، يحد ب 30-50
انتقام، مما يعني انتقام انه انتهى ال telomere وبعد
signal الى ايقاف عملية الانتقام. طب في عينا خلايا
ري Sperm, Blood, Bone marrow germ cell ينتقم استمرار، طب
ثم اكل في عيني enzyme موجود فيم الخلايا مدة
تحت telomerase، بعد كل انتقام الجزء التي تضربها
بغير تكوينه + في لوز اللوز لا cancer + هابنوت من انتقام

* نبتة في من أكر من جهة مكن) جينا موهنوعى انفاق الحقن
على ال apoptosis (apoptotic effect) على الية تضاعف
تسريع الاضداد الخبية

" الية عرقه ية كفاية. في تقابل كثر، بس حيل كفاية "

We can use Immunohistochemistry to detect defects in genes and molecules

Morphologically: (Adenocarcinoma)

- Rt is brider than Lt $\rightarrow$ so more cancer possibility
in Right side

وقبل الامام كبر قد عنة obstruction

Rectal bleeding

↓

مكن - mass

↓

مكن ulcerated

- Left easy to become obstructed

Hemorrhoids

- affect about 5% of general population

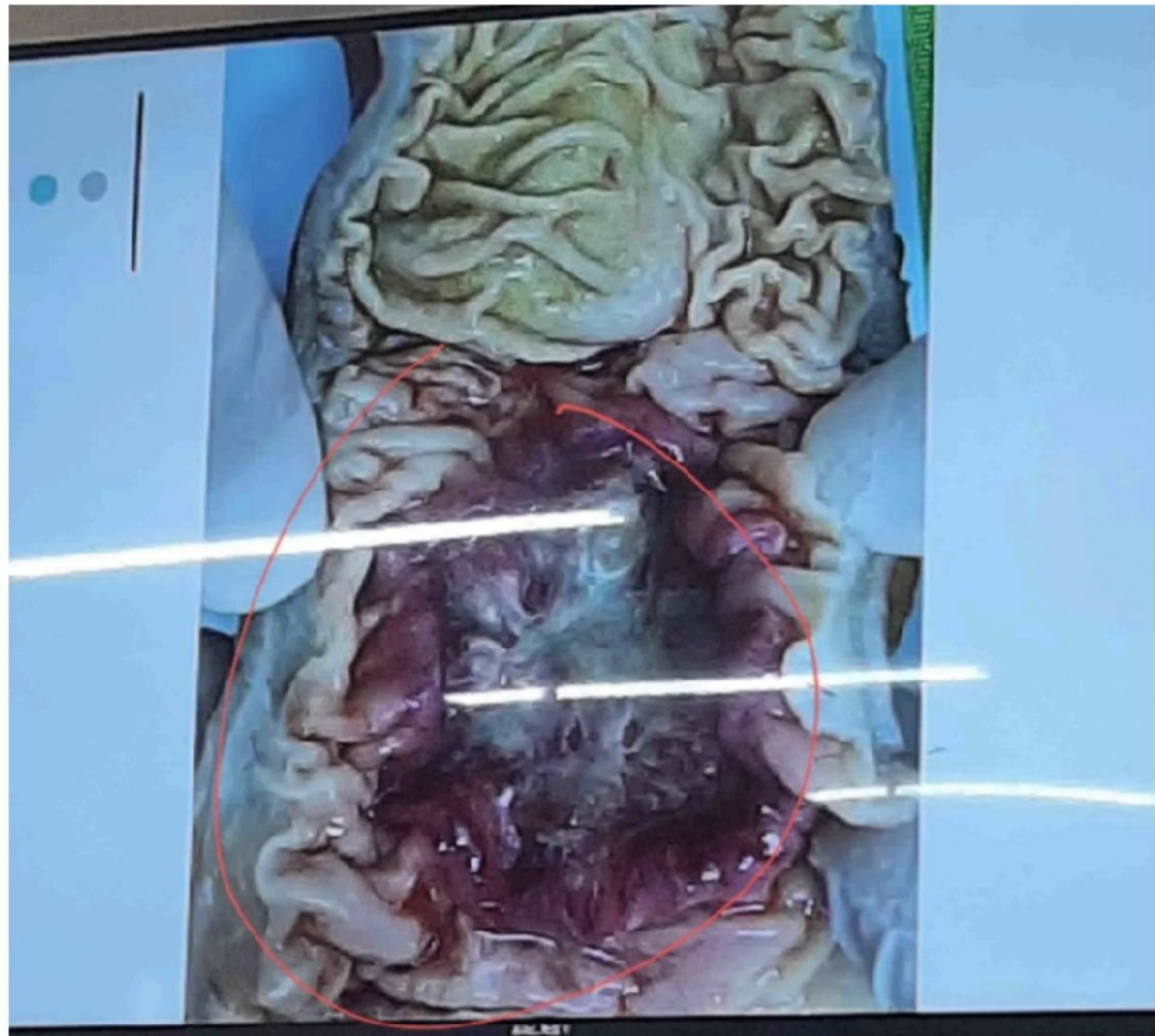
- develop secondary to persistently elevated venous pressure within Hemorrhoidal plexus.

- In constipation and venous stasis of pregnancy and also secondary to hypertension

- present with pain & rectal bleeding

Heba Edwar





No
Neurovascular
alteration
 at 2-Trial
 Proteolytic Enzymes
 vs.
 FCA
 FE