Small and Large Intestinal pathology, part 4

1 Colonic Adenocarcinoma

▶Most common malignancy of the gastrointestinal tract
(the most common tumors in the intestine are in the colon)
▶Small intestine is uncommonly involved by neoplasia.
▶Peak: 60 to 70 years→a disease of elderly
▶ Developed countries lifestyles and diet.(red meat)
▶ Low intake of vegetable fiber and high intake of carbohydrates and fat.
▶ Aspirin or other NSAIDs have a protective effect. (these drugs inhibit the cyclooxygenase and suppress the epithelial proliferation)
▶Cyclooxygenase-2 (COX-2) promotes epithelial proliferation

Pathogenesis
▶Heterogeneous molecular events (Multifactorial and multiple genes are involved
▶Sporadic > familial
▶Two genetic pathways:(involved in both the sporadic and familial types of colonic adenocarcinomas)
1- APC/β-catenin pathway >> increased WNT signaling (remember APC gene are involved in Adenomatous Polyposis coli syndrome (FAP Syndrome))
2- Microsatellite instability pathway due to defects in DNA mismatch repair (remember it's involved in HNPCC (LYNCH Syndrome) as a familial cancer syndrome)

1 The APC/β-catenin pathway: also called chromosomal instability
▶ It's classic pathway involved in classic adenoma carcinoma sequence.
▶80% of sporadic colon tumors
▶The development of adenoma and the progression to adenocarcinoma involve APcatenin pathway activation
▶Mutation of the APC tumor suppressor gene: EARLY EVENT
▶APC is a key negative regulator of β-catenin, a component of the WNT signaling pathway (beta catenin will be activated and accumulated along with the WNT signaling pathway)
▶ both copies of APC should be inactivated for adenoma to develop (1st and 2nd hits)
▶Pathway:• Loss of APC >>> accumulation of B-catenin >> enters nucleus >> MYC and cyclin-D1 transcription >> promote proliferation.
• Additional mutations >> activation of KRAS oncogene (LATE EVENT) (seen more in large and invasive adenomas
• SMAD2 and SMAD4 mutations (tumor suppressor genes.)
• TP53 (tumor suppressor gene) is mutated in 70% -80% of colon cancers (LATE EVENT IN INVASIVE)(not seen usually in early small adenomas)
• TP53 inactivation mutation
• Later on >> Expression of telomerase also increases as the tumor advances.
*****Check pic 1*****

2 The microsatellite instability pathway
▶DNA mismatch repair deficiency
▶ Loss of mismatch repair genes
▶Mutations accumulate in microsatellite repeats((This Instability has a devastating effect on the tumor development not only in colorectal carcinoma but also in other types of cancer like in HNPCC))
▶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)
*****check pic 2 & table*****

MORPHOLOGY

Macroscopic
▶Proximal colon tumors: polypoid, exophytic masses(protruding to the lumen of the colon)
▶Proximal colon: rarely cause obstruction(wide lumen of the caecum)
▶Distal colon: annular lesions "napkin ring" constrictions & narrowing

Microscopic
▶Dysplastic and invasive GLANDS with strong desmoplastic response
(which is a fibroblastic proliferation , collagen deposition and edema formation around the invasive gland).
▶Necrotic debris (dirty necrosis) are typical.
▶Some tumors give abundant mucin or form signet ring cells.(like in the stomach)
****note: Dysplastic glands can also be seen in adenomas, but the Dirty necrosis and the Desmoplastic response indicate an invasion and carcinoma

Clinical Features
▶ Endoscopic screening >> cancer prevention (in western countries, they offer colonoscopic screening for all patients above the age of 50 Also endoscopic screening can be offered for patients with family history ((early detection so the treatment is possible))
▶Early cancer is asymptomatic !!!!!!!! (and this leads to late discovery of the cancer especially if it was cecal and right sided colon cancers
▶ Cecal and right side cancers: Fatigue and weakness (iron deficiency anemia)
▶ Iron-deficiency anemia in an older male (>50) or postmenopausal female is gastrointestinal cancer until proven otherwise.
▶Left sided carcinomas: occult bleeding, changes in bowel habits, cramping left lower quadrant discomfort.
****note :occult bleeding is not visible bleeding detected by a test (stool occult blood test)
▶ Poor differentiation (the tumor is ugly and doesn't form glands) and mucinous histology > > poor prognosis (not the most important prognostic factors)
▶Most important two prognostic factors are 1- Depth of invasion 2- Lymph node metastasis.
▶Distant metastases (lung and liver) can be resected.((liver whitish nodules (metastatic foci for colon carcinoma))
▶Staging of colorectal cancer 1. T-depth of invasion. 2. N-spread to regional lymph nodes 3. M- distant metastasis

2 Appendix

General ▶Normal true diverticulum of the cecum
▶ACUTE APPENDICITIS (very common)
▶TUMORS OF THE APPENDIX (rare)

ACUTE APPENDICITIS

▶Most common in adolescents and young adults.
▶May occur in any age.
▶The symptoms that the patient presents with are similar to other diseases so it's Difficult to confirm (do appendectomy even the suspicion is 70%)

diseases that may present in symptoms like the appendicitis
▶Mesenteric lymphadenitis(viral inflammation of the mesenteric lymph nodes
▶Acute salpingitis (inflammation of the Fallopian tube)
▶Ectopic pregnancy(pregnancy outside the uterus)
▶Mittelschmerz(mid-cycle pain) (pain associated with ovulation),
▶(Para ovarian or para tubal)Ovarian cysts torsion or rupture Meckel diverticulitis sometimes there is inflammation so symptoms mimic appendicitis) and Crohn disease
Clinical note :
• Take a good history from the patient, asking about the date of the last menstrual cycle could give a clue.
• Female in the reproductive age with symptoms like appendicitis must be first sent to gynecology department to be sure that there is no gynecologic problems.

Causes:
▶ Luminal obstruction in 50-80% of cases >> increased luminal pressure >> impaired venous drainage >>congestionand ischemic injury & stasis associated bacterial proliferation >>> inflammatory response rich in neutrophils & edema.
▶ Obstruction by fecalith (most common) , less commonly : gallstone, tumor, worms…

▶The gold standard histopathologicDiagnosis requires neutrophilic infiltration of the muscularis propria ▶No neutrophils→Not appendicitis
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▶Acute suppurative appendicitis >> more severe (extensive neutrophils infiltration) >> focal abscess formation.
▶Acute gangrenous appendicitis >> necrosis and ulceration.
Note :we can have appendicular perforation if the patient is not diagnosed early and the inflammation continues with perforation >> results in peritonitis **

Clinical Features
▶Early acute appendicitis: periumbilical pain (referred pain)
▶Later: pain localizes to the right lower quadrant
▶Nausea, vomiting, low-grade fever, mildly leukocytosis (elevation of WBCs)
▶ A classic physical finding is McBurney's sign (McBurney's point).
▶Signs and symptoms are often absent, creating difficulty in clinical diagnosis. (Sometimes you should send the patient to the radiology)

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 most cases considered benign tumors
▶Nodal metastases & distant spread are rare.(even the association with carcinoid syndrome is not common because carcinoid syndrome to occur needs a metastatic tumor)
▶Have a good prognosis

Gross appearance:
Yellowish-well circumscribed Mass in the tip of the appendix
microscopic appearance:
Nesting pattern, abundant cytoplasm, salt and pepper chromatin similar to other neuroendocrine tumors that had been discussed earlier.

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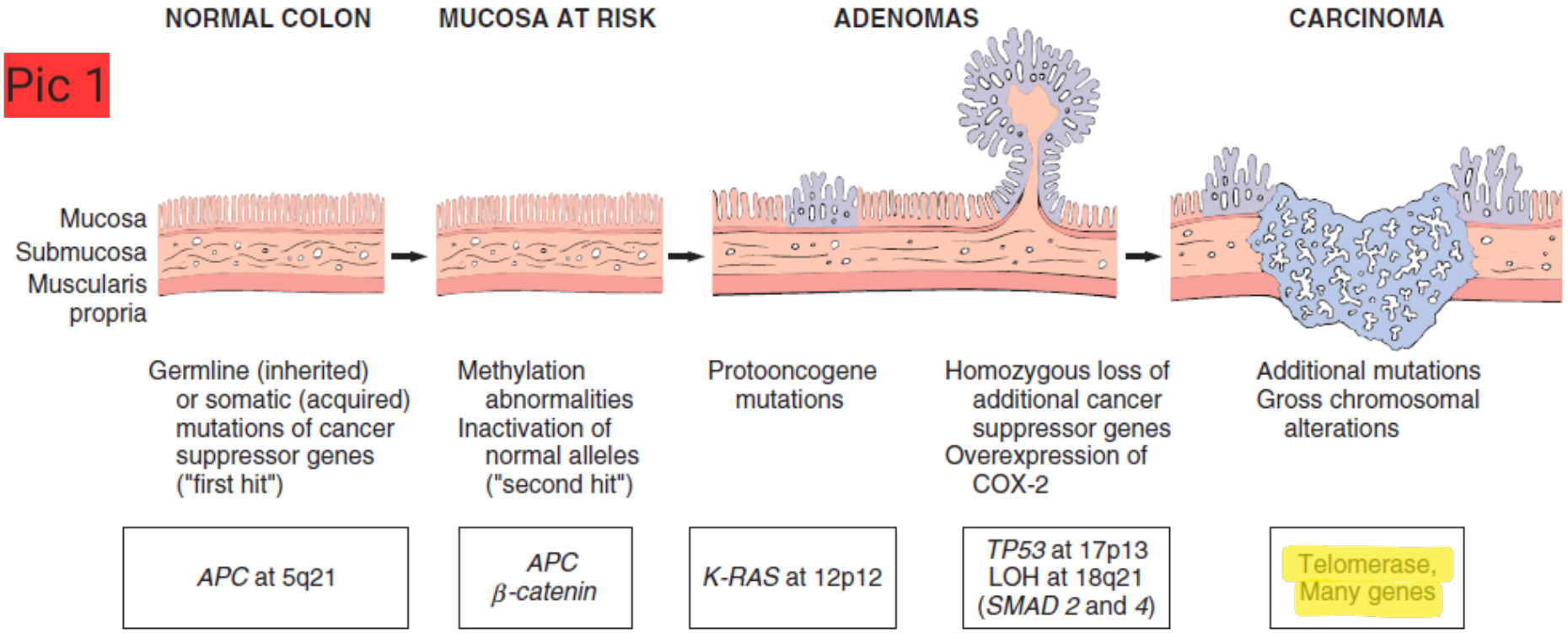
Pic 1

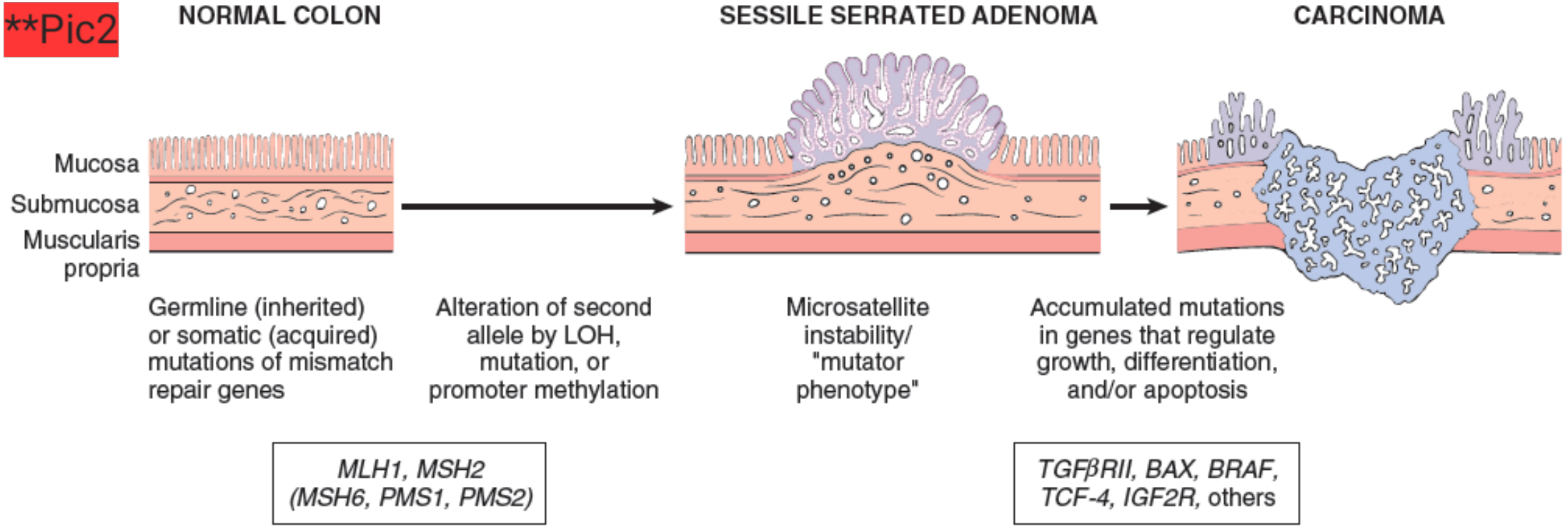


• If a patient had the Germline mutation which can be inherited in familial cases like in (FAP) for ex , then he needs another copy of the gene to be mutated which can take place in a short time so here the tumor will appear at an earlier age since we already have the first hit inherited and the second mutation hit will appear later in life • In sporadic cases we have the somatic mutation which is acquired later in life then we should have the second mutation to be acquired so this will take longer time and this is why familial cancers appear earlier than sporadic

→ 1st HIT mutation in APC gene, the 2nd HIT should take place resulting in beta catenin accumulation in cytoplasm so here the Mucosa is at risk (the mucosa starts its transformation) (note that we still don't have adenoma or dysplasia so these events occur very early even before the formation of a colonoscopically detected mass or lesion)

Then we will have later event which is K-RAS mutation which is Protooncogene so the development of adenoma will start as you can see in the 3rd picture in the figure , it starts very small then it will enlarge forming the large colonic adenoma. (As the adenoma enlarges as the risk for progression increases), then other mutations will accumulate like TP53, SMAD2&4 Later on, when the tumor becomes invasive (grossly visible cancer) →more mutations – more chromosomal alterations will appear & the telomerase will be activated

**Pic2



• As we said , this pathway starts with a mutation in DNA mismatch repair genes which are multiple genes including MLH1, MSH2, MSH6, PMS1 and PMS2 . So, the mutation in these genes could be a germline mutation (inherited) like in HNPCC or a somatic (acquired) mutation like in sporadic colorectal carcinoma, then the 2nd copy of the gene should be altered in order for subsequent steps to take place like the first and second hits in APC beta catenin pathway so both copies should be inactivated , leading to microsatellite instability which results in forming a peculiar special type of adenoma and it's different from the adenoma formed in the 1st pathway "APC/Beta Catenin" →The adenoma here is known as sessile serrated adenoma (it's not ordinary adenoma) which also has risk of transformation to an invasive adenocarcinoma by acquisition of more mutations in different genes involving apoptotic and cell proliferation genes

table

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	DNA mismatch repair	*MSH2, MLH1*	Autosomal dominant	Right side	Sessile serrated adenoma; mucinous adenocarcinoma
Sporadic colon cancer (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

- This table summarizes almost all what we have said about the mechanism &the pathogenesis of colorectal cancer >> memorize it well
- Remember that we have sporadic cancer and familial cancer (FAP and HNPCC syndrome)
- colonic adenocarcinoma is sporadic most of the time (80% involve the APC /WNT pathway and 10 to 15 % involve the DNA mismatch repair pathway which also seen in lynch syndrome)
- The sessile serrated adenoma is more commonly seen in the DNA mismatch repair genes pathway
- More classical adenomas (left side involvement) are typical for sporadic colon cancer