GIS 8

PATHOLOGY

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this sheet will cover the last topic related to intestinal pathology which includes

- Colonic Adenocarcinoma
- Acute Appendicitis
- Tumors of the appendix

Colonic Adinocarcinoma

- It is the most common malignancy of the gastrointestinal tract (remember that the most common tumors in the intestine are in the colon) so the small intestine is uncommonly involved by neoplasia.

- The peak age is between **60 to 70** years → a disease of elderly so the risk is increased with increasing age. However, 20% of patients are **under** the age of **50**

- It is more common in **developed countries** due to their lifestyles and diet that is low in vegetable fibers and high in carbohydrates and fat, and there is ongoing evidence that the **red meat** associated with an **increased risk** with colonic adenocarcinoma.

- Diet is very important risk factor carrying in it the carcinogens, that are the driving force for the development of the disease

- Aspirin and NSAID have a **protective** effect but why? It is well known that cyclooxygenase II promotes epithelial proliferation and these drugs inhibit the cyclooxygenase and suppress the proliferation

Pathogenesis

- Heterogeneous molecular events→ Multifactorial and multiple genes are involved →during the process of CA development there is an accumulation and acquisition of multiple mutations

- **Sporadic** cases are more common than familial cases (sporadic malignancies>>> familial)

- **T**wo Genetic Pathways for the development of the carcinoma. Those pathways are involved in both the sporadic and familial types of CA

  1. **APC/Beta Catenin pathway** which involves the APC Beta Catenin genes (remember we mentioned APC gene involvement in Adenomatous Polyposis coli syndrome (**FAP Syndrome**) & the mutation in these genes lead to increasing WNT signaling promoting cancer development
  2. **Microsatellite Instability pathway**
     (remember it's involved in HNPCC "LYNCH Syndrome")
     Microsatellite instability is the consequence of defects in the DNA mismatch repair genes which are the genes responsible for the correction of any error that occurs during DNA replication → **Acquisition of different t mutations leading to colorectal carcinoma**

APC/Beta Catenin pathway

- Also called **chromosomal instability pathway**

- It's involved in 80% of sporadic colonic cancer cases **(more common than the microsatellite instability pathway)**

- Involved in **classic adenoma carcinoma sequence** (We said in the previous lecture that colonic adenoma is precursor of most types of Colonic Adenocarcinoma)

- The development of adenoma and the progression of the adenoma to carcinoma involve the APC beta catenin pathway activation

- First, we have mutation in the APC gene (tumor suppressor gene) and **this is a very early event in this pathway**

- The **APC** gene is a **negative regulator** of other gene called the **Beta Catenin gene** which is a component of **WNT signaling**. As a result, we lose this negative regulation in the mutated APC and the beta catenin will be activated along with the WNT signaling pathway.

- The **question** is: Can we have adenoma if only one copy of APC gene is mutated? **NO** as **both copies** of APC gene should be inactivated for the adenoma to develop so we need **both** the first copy mutation "1st hit" and the second copy mutation "2nd hit".

- Then the level of beta catenin will increase so there will be accumulation of it in the cytoplasm of the cell and by entering to the nucleus it leads to the **transcription** of certain genes which are the **MYC** and **Cyclin- D1** **genes** which result in **proliferation of the cells**

- Additional accumulation of mutations will result in the activation of **KRAS gene** which is considered a **late event** in the carcinogenesis and this activation will lead to the **inhibition of apoptosis**

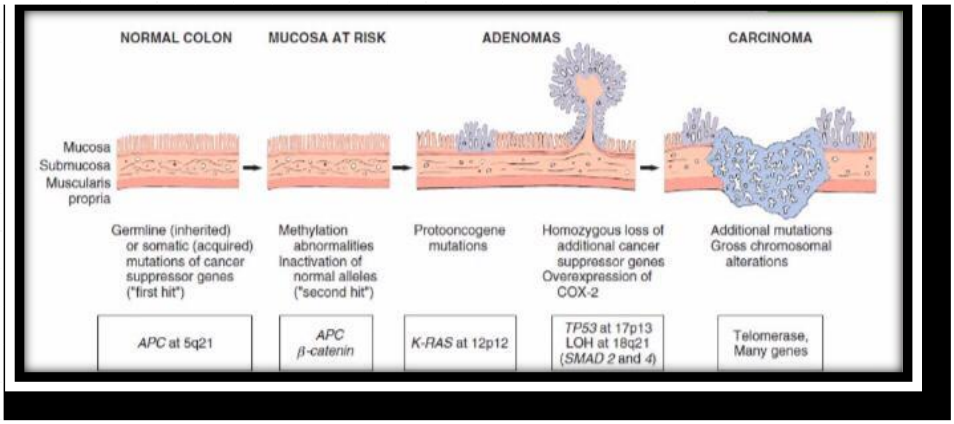
- The result is **cellular proliferation** and **inhibition of apoptosis** so the **cells will live longer** leading to tumor development

- Other genes that are also mutated in this process which are the **SMAD2** And **SMAD4** which are considered tumor suppressor genes

- Then in a **very late event** in carcinogenesis becomes the **TP53** mutation (inactivation) This gene is mutated in 70%-80% of **colon cancer** but as we said that this mutation is a late event in the carcinogenesis and usually occurs when the tumor transforms into an **invasive** tumor

- Also, there will be expression of **telomerase** which increases as the tumor advances

- APC gene mutation → Beta Catenin accumulation → Beta Catenin enters the nucleus → Activation (transcription) of MYC and Cyclin-D1 → Proliferation will start → Additional mutations will accumulate like KRAS gene leading to inhibition of apoptosis → SMAD2 & SMAD4 & TP53 mutations will take place



The figure above illustrates the APC/Beta Catenin pathway

- If a patient had the **Germline mutation** which can be inherited then he needs another copy of the gene to be mutated 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 but still the tumor will appear at an earlier age

- In sporadic cases we have the somatic mutation which is acquired later in life→ 1st HIT mutation in APC gene, the 2nd HIT should take place resulting in beta catenin accumulation so here the Mucosa is **at risk (the mucosa starts its transformation)**

- Beta Catenin enters the nucleus promoting the transcription of genes that lead to cell proliferation followed by K-RAS mutation which is Protooncogene so the development of adenoma will start as you can see in the 3rd picture in the figure above it starts very small then it will enlarge forming the large colonic adenoma. Then other mutations will accumulate like TP53, SMAD2&4

- Also, there will be overexpression of **COX-II** and that's why aspirin has a protective role against colonic cancer because it counteracts the effect of COX-II so it can delay or prevent cancer formation

- Later on, when the tumor becomes invasive → more mutations – more chromosomal alterations will appear & the telomerase will be activated

Microsatellite Instability Pathway

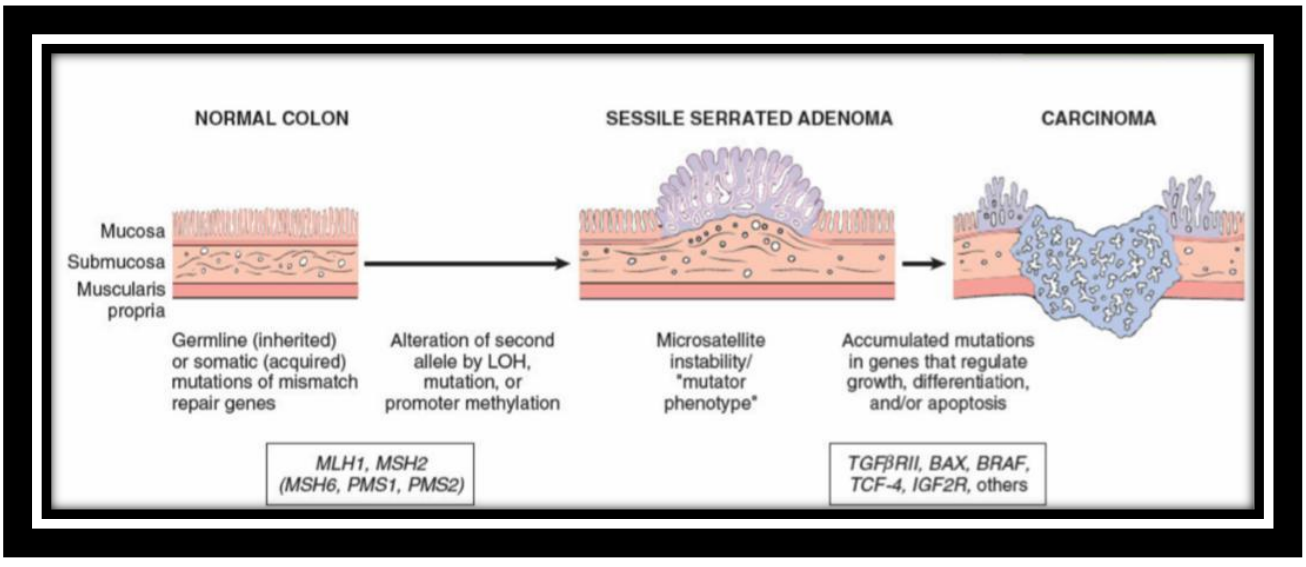
- Involves the **DNA mismatch repair genes**

- Genes lost→ Accumulation of mutations in the **microsatellite repeats** of the DNA which are a short repeats of DNA nucleutides leads to their instability (think of it as they are loaded with many mutations, and additional mutations will be acquired upon further divisions of the cell)

- 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

- If those microsatellites are located in **noncoding regions** of the gene **there will be silent mutation**

- If they are in coding or the promoter area of the gene especially genes that are involved in **cell growth** and apoptosis like **TGF-beta** and **BAX genes** this will lead to uncontrolled cell growth and inhibition of apoptosis



- 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 Germline mutation like in HNPCC or a somatic mutation like in sporadic colorectal carcinoma then the 2nd copy of the gene should be altered leading to microsatellite instability which result 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 involving apoptotic and cell proliferation genes

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

Numerous colonic adenomas with 100% transformation risk to adenocarcinoma

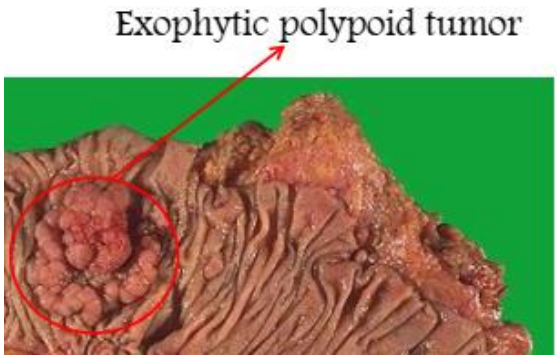
*This table is very important

- This table summarizes all the causes and the molecular events in the colonic adenocarcinoma
- Remember that colonic adenocarcinoma is sporadic most of the time
- (80% of cases) and inherited in about 10%-20% of in cases associated with inherited familial colorectal carcinoma syndrome like FAP and HNPCC syndrome
- The **right** side of colon is preferred in **DNA mismatch repair gene involvement**
- The sporadic colon cancer accounts for 80% of colorectal cancer cases and prefers the **left** side of colon
- All carry risk of malignancy (adenocarcinoma) with different genetic pathways

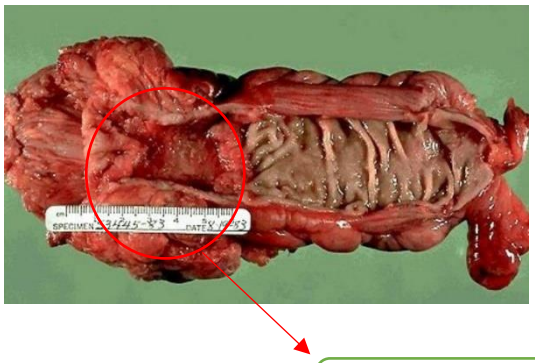
MORPHOLOGY

1-Macroscopic

- Upon macroscopic examination of the colon, many differences between the proximal and distal parts of the colon will take place
- In **Proximal colon**, polypoid (multiple polyps), and exophytic masses will be present
- In **Distal colon**: annular lesions "napkin ring" constrictions & narrowing (the second picture shows the napkin ring)

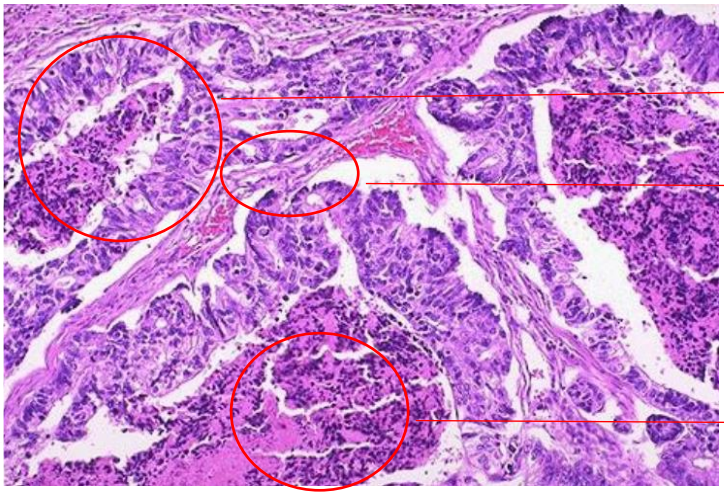


- Colorectal cancer in the proximal colon **rarely cause obstruction**, this is due to the wide diameter of the proximal colon compared to the distal part (obstruction is more common in the distal part)
- Remember, in medicine there is no absolute, so exophytic mass may present on the distal part and vice versa



2-Microscopic

- Dysplastic GLANDS with strong desmoplastic response. (desmoplastic response is a fibroblasts proliferation around the invasive gland)
- Dirty Necrosis is very common in colorectal carcinoma
- Some tumors give abundant mucin or form signet ring cell (filled with mucin)
- Dysplastic Gland + Dirty necrosis+ Desmoplastic response = Colorectal carcinoma
- Dysplastic glands can also be seen in adenomas, but the Dirty necrosis and the Desmoplastic response indicates an invasion and carcinoma



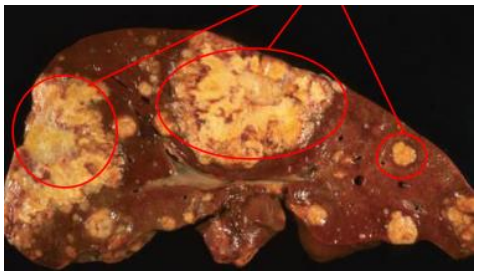
Clinical Features

- The most important step in management of the colorectal carcinoma is the prevention and early detection, by endoscopic or colonscopic screening for elderly patients (>50), and for those who are at high risk such as a remarkable family history (a young family member with colorectal cancer could indicate a FAP)
- Early cancer is asymptomatic, and this leads to late discovery of the cancer especially if it was cecal and right sided colon cancers (no obstruction of the intestine)
- **Right Sided cancer** → Fatigue and weakness
  → **Iron-deficiency anemia**
- Iron-deficiency anemia is caused by the continuous minimal loss of blood from the intestine (loss of RBC exceeds production)

- **Left sided carcinomas** → occult bleeding
  → changes in bowel habits
  → cramping left lower-quadrant discomfort

- occult bleeding is not visible bleeding to the patient or physician, no remarkable fresh blood within the stools, although some tumors may present with fresh blood, detected in stool samples
- **Iron-deficiency anemia in an older male or postmenopausal female is gastrointestinal cancer until proven otherwise**

Prognosis



Most important two prognostic factors are

1- **Depth of invasion**

Whether the tumor stays in mucosa or reaches submucosa or MP or serosa.

The deepest the tumor, the worst the prognosis

2- **Lymph node metastasis**

* Distant metastases are usually to the lung and the liver, and can be resected
* Multifocal metastasis is a dismal prognosis
* Poor differentiation and mucinous histology >> poor prognosis

***Staging of colorectal cancers**

1. T-**depth of invasion**; tumors limited to the mucosa generally do not spread due to lack of lymphatics in the mucosa. (from PATHOMA and not mentioned by Dr.)
2. N-**spread to regional lymph nodes**
3. M- **distant spread**

Appendix

- Normal true diverticulum of the cecum
- Two Abnormalities will be discussed → ACUTE APPENDICITIS
  → ACUTE APPENDICITIS

ACUTE APPENDICITIS

- Most common in adolescents and young adults, but may occur in any age
- Difficult to confirm preoperatively because the symptoms aren't always easy to give a differential clue- sometimes the patient has a central abdominal pain so it's not always RLQ pain which is typical for this disease.

- The followings are diseases that may present in symptoms like the appendicitis, but they are not (Differential Diagnosis)

1- **Mesenteric lymphadenitis** → Viral infection of the mesentery, when the surgeon opens the abdomen, he will find a normal appendix, but the surrounding lymph nodes will be inflamed due to the infection

2- **Acute salpingitis** → Acute inflammation for the fallopian tubes especially in the females in the reproductive age

→ A female in the reproductive age with symptoms like appendicitis must be first sent to gynecology department to be checked for this inflammation

3- **Ectopic pregnancy** →Especially if it was in the fallopian tube

4- **Mittelschmerz pain** →pain associated with ovulation (mid-cycle pain)
→ Pain in the middle of the menstrual cycle
→ Take a good history from the patient, asking about the date of the last menstrual cycle could give a clue

5-**Meckel diverticulitis**

6- **Para-ovarian or Para-tubal cysts when rupture/twist**

* 70% of appendectomy cases have a truly inflamed appendicitis, and 30% of cases there is no inflamed appendix (acceptable percentage)-the physician must have a high index of suspicion for appendicitis

* Acute appendicitis in elderly must alarm you with the underlying cause, such as colorectal cancer that may obstruct the base of the appendix, leading to its inflammation (why does he have acute appendicitis at this age?)

PATHOGENISIS

1- Luminal obstruction in 50-80% of cases
Mainly due to fecalith & less commonly by gallstone, worms, tumor (especially in elderly)
2- increased luminal pressure
3- impaired venous drainage
4- ischemic injury & stasis (decreased blood flow) associated bacterial proliferation
5- inflammatory response rich in neutrophils & edema

* Acute appendicitis is not considered a bacterial infection, but the bacterial proliferation is a consequence of the appendiceal obstruction.

Diagnosis

*The gold standard diagnosis requires neutrophilic infiltration of the muscularis propria (neutrophils may be present in the mucosa or submucosa)

*No neutrophils→ Not appendicitis

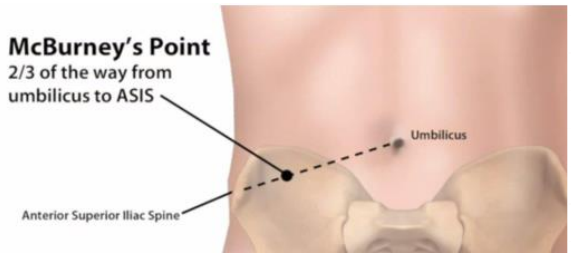
*The appendectomy is performed even when the surgeon is not 100% sure that the case is truly appendicitis → to avoid perforation and PERITONITIS

* Acute suppurative appendicitis → more severe form with massive neutrophilic infiltration>> focal abscess formation

* Acute gangrenous appendicitis >> necrosis and ulceration of the appendix

Clinical Features

- **Early** acute appendicitis: periumbilical pain (start as referred pain)
- **Later**: pain localizes to the right lower quadrant
- Nausea, vomiting, low-grade fever, mildly leukocytosis (not seen in all patients)
- **McBurney's sign** → severe pain felt by the patient when you apply a pressure on McBurney's point (the patient may scream)
- **McBurney's sign is absent early in the disease**
- Signs and symptoms are often absent, creating difficulty in clinical diagnosis



TUMORS OF THE APPENDIX

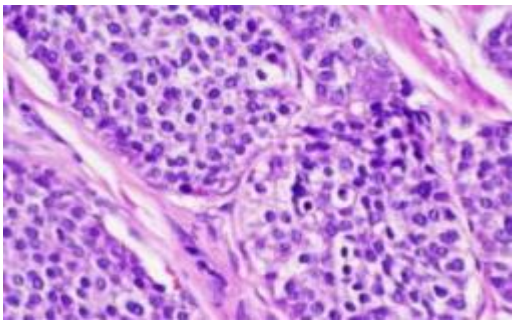
υ These tumors are very rare

υ The most common tumor: *carcinoid* (neuroendocrine tumor)

υ **Incidentally** found during **surgery** (appendectomy)or on examination of a resected appendix

υ Distal tip of the appendix is the common site

υ Nodal metastases & distant spread are rare →in most cases considered benign tumors



Yellowish-well circumscribed
Mass in the tip of the appendix

Nesting pattern, abundant cytoplasm, salt and pepper chromatin similar to other neuroendocrine tumors that had been discussed earlier.

"Thank you all, I love you all, Have a great weekend" Dr. Maher Alhadidi