Pathology

# Pathology sheet

DONE BY: MAEN FAOURY
Bowel obstruction and tumors

Intestinal Obstruction

• Obstruction of the GI tract may occur at any level, but the small intestine is most often involved because of its relatively narrow lumen.

• Causes:
  • Hernias
  • intestinal adhesions
  • Intussusception
  • volvulus
  • Tumors
  • Infarction—— strictures
  • Crohn disease—— strictures
The clinical manifestations of intestinal obstruction include:

- abdominal pain and distention
- Vomiting
- Constipation

Most important manifestations: abdominal pain and vomiting.

The type of vomiting will determine the location of the obstructions,

- Green material → bile content → the obstruction is in the small Bowel.

- Hernias:
- Hernias are the most frequent cause of intestinal obstruction worldwide.

  - Any weakness or defect in the abdominal wall may permit protrusion of a hernia sac (serosa-lined pouch of peritoneum)

- Inguinal and femoral canals, umbilicus, or at sites of surgical scars.

  - Small bowel loops are typically involved, but omentum or large bowel may also protrude, and any of these may become entrapped.

  - Incarceration (permanent entrapment)

  - Strangulation (arterial and venous compromise)

  - Infarction

Hernia sac: peritoneum surrounding the bowel, it will cover the area that developed hernia, it is used to diagnose hernia microscopically.

3 stages of Hernia:

1. Incarceration: at the beginning hernia will be reversible
   (بتدخل وبتطلع من الinguinal canal مثلا)
   - Once it enters the canal without getting out → Incarceration (permanent entrapment)

2. Strangulation: if there was no treatment to the hernia
   → Cut of blood supply, venous and arterial, patient will come with severe abdominal pain (no infarction).
- 3. Infarction: if there was no treatment to strangulation, infarction will develop.
- Strangulation is reversible with treatment but in infarction we must remove the loop that has Hernia.

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- **Adhesions:**

- causes: Surgical procedures, peritoneal inflammation (such as infection, endometriosis)
- resulting in internal herniation
- Fibrous adhesions are most often acquired, but can be congenital in rare cases. Therefore, internal herniation must be considered even in the absence of a history of peritonitis or surgery.

Adhesions: fibrous tissue between loops of bowel. You must ask the intestinal obstruction patient if he had any procedures in the past (like cesarean section with females) fibrous band will create Internal herniation between loops which will create bowel obstruction.

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- **Volvulus:**

- Twisting of a loop of bowel about its mesenteric point of attachment is termed volvulus; it results in both luminal and vascular compromise.
- It occurs most often in large redundant loops of **sigmoid colon**, followed in frequency by the cecum, small bowel, stomach, or, rarely, transverse colon.
Volvulus: cut of the blood supply and obstruction

- **Intussusception:**
  - Intussusception occurs when a segment of the intestine, constricted by a wave of peristalsis, telescopes into the immediately distal segment. Once trapped, the invaginated segment is propelled by peristalsis and pulls the mesentery along.
  - Intussusception is the most common cause of intestinal obstruction in children younger than 2 years of age.
  - Some cases are idiopathic, but many cases have been associated with viral infection and rotavirus vaccines, perhaps due to reactive hyperplasia of Peyer patches and other mucosa-associated lymphoid tissue which can act as the leading edge of the intussusception.
  - Intussusception is rare in older children and adults, and is generally caused by an intraluminal mass or tumor that serves as the initiating point of traction.

A children will come with constipation and then bloody diarrhea and vomiting. Intussusception: telescoping of one loop into another so it will cause obstruction.

Why it is more common in children? because of vaccines
Normally in small bowel we have Peyers patches, in children peyer patches are hyperplastic, forming a mass especially while taking vaccines; because of the reactivation of the immune system.

it could also develop without taking vaccines because of viral infections.
It’s not dangerous if a children under 2 years of age comes with Intussusception, but if the patient is older it could be because of tumors.

Sigmoid Diverticular Disease

• Pseudodiverticula: outpouchings of the mucosa and submucosa
• true diverticula: such as Meckel diverticulum, invested by all three layers of the colonic wall.
• Diverticula are generally multiple and the condition is referred to as diverticulosis.
• Where nerves, arterial vasa recta, and their connective tissue sheaths penetrate the inner circular muscle coat, focal discontinuities in the muscle wall are created. In other parts of the intestine these gaps are reinforced by the external longitudinal layer of the muscularis propria, but, in the colon, this muscle layer is gathered into the three bands termed taeniae coli. Increased intraluminal pressure is probably due to exaggerated peristaltic contractions, with spasmodic sequestration of bowel segments, and may be enhanced by diets low in fiber, which reduce stool bulk, particularly in the sigmoid colon.

Do not cause obstruction
Diverticula: protrusion of mucosa, submucosa with or without muscularis propria into intestinal wall.
Usually in old aged patients ≥ 60 years old, diet low in fiber will lead to constipation, during defecation there will be straining → intraluminal pressure in areas with defect (where there is blood supply; veins and nerves) there will be invagination → Pseudodiverticula.
The patient will be a-symptomatic.
If there is an inflammation (diverticulosis) there will be symptoms like abdominal pain and if complications like perforation happen it will lead to acute abdomen. The problem is when complications happen.

• Clinical Features:

• More in Western adult populations older than age 60.

• Most individuals with diverticular disease remain asymptomatic throughout their lives.

• However, about 20% of individuals with diverticuli develop manifestations of diverticular disease, such as intermittent cramping, continuous lower abdominal discomfort, constipation, distention, or a sensation of never being able to completely empty the rectum. Patients sometimes experience alternating constipation and diarrhea that can mimic IBS. Occasionally there may be minimal chronic or intermittent blood loss, and, rarely, massive hemorrhage.

**Meckel diverticulum**

• Meckel diverticulum occurs as a result of failed involution of the vitelline duct, which connects the lumen of the developing gut to the yolk sac.

• rule of 2s:

• - Occur in approximately 2% of the population

• - Are generally present within 2 feet (60 cm) of the ileocecal valve
• Are approximately 2 inches (5 cm) long
• Are twice as common in males
• Are most often symptomatic by age 2
• Symptoms: bleeding, obstruction

Meckel diverticulum (true): congenital anomalies because of persistent of vitelline duct (connect between the gut and yolk sac)

Normally involution happens to it but if not meckel diverticulum will develop

Gastric mucosa → bleeding

Polyps

• Polyps are most common in the colo-rectal region but may occur in the esophagus, stomach, or small intestine.

• Intestinal polyps can be classified as non-neoplastic or neoplastic in nature.

• The most common neoplastic polyp is the adenoma, which has the potential to progress to cancer.

• The non-neoplastic polyps can be further classified as inflammatory, hamartomatous, or hyperplastic.

Polyps: elevation in the mucosa

Grossly Classification:

• Pedunculated polyp: with stalks (جذع)

• Sessile polyp: without stalks (just an elevation)
• **hyperplastic Polyps:**

- The pathogenesis of hyperplastic polyps is incompletely understood, but they are thought to result from decreased epithelial cell turnover and delayed shedding of surface epithelial cells.

- It is now appreciated that these lesions are **without malignant potential**.

- most commonly found in the left colon

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**Figure 17-41** Hyperplastic polyp. **A**, Polyp surface with irregular tufting of epithelial cells. **B**, Tufting results from epithelial overcrowding. **C**, Epithelial crowding produces a serrated architecture when crypts are cut in cross-section.

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Incidental finding
Increase cell build up but decrease in turnover, hyperplastic crypts (serration) mercedes benz look.

The serration will be in some of the crypts not all of them.

If the serration was in all crypts it is called serrated polyp.

• **Hamartomatous Polyps:**
  - Hamartomatous polyps occur sporadically or as components of various genetically determined or acquired syndromes.
  - **Juvenile Polyps:**
    - May be sporadic (solitary lesions) or syndromic (3 to as many as 100 polyps, AD disorder, 30% to 50% of patients with juvenile polyposis develop colonic adenocarcinoma by age 45).
    - Occur in children younger than 5 years of age, Most juvenile polyps are located in the rectum, typically present with rectal bleeding.

**Peutz-Jeghers Syndrome:**
This rare autosomal dominant syndrome presents at a median age of 11 years with multiple GI hamartomatous polyps and mucocutaneous hyperpigmentation.

The polyps of Peutz-Jeghers syndrome are most common in the small intestine.

Associated with a markedly increased risk of several malignancies.

If a patient comes to you with lower GI bleeding, and you order a lower GI endoscope that showed polyps, after studying the polyps in pathology lab the results showed Hamartomatous
polyps, we must exclude some diseases: **Peutz-Jeghers Syndrome and - Juvenile Polyposis**

If the patient had skin pigmentation in the oral mucosa and around the anus→ **Peutz-Jeghers Syndrome**

But if the patient was younger than 5 years with lower GI bleeding and Hamartomatous polyps (100 in number) we think of **Juvenile polyposis syndrome**

We don’t call it a syndrome if it was Hamartomatous polyps alone, it must be with another manifestations.

Polyps alone we remove them easily but syndrome increases the malignancy in GI and extra intestinal.

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Mean Age at Presentation (yr)</th>
<th>Mutated Gene(s); Pathway</th>
<th>Gastrointestinal Lesions</th>
<th>Selected Extra-Gastrointestinal Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juvenile polyposis</td>
<td>&lt;5</td>
<td>SMAD4, EMPT1; TGF-β signaling pathway</td>
<td>Juvenile polyps; risk of gastric, small intestinal, colonic, and pancreatic adenocarcinoma</td>
<td>Congenital malformations, digital clubbing</td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td>10-15</td>
<td>STK11; AMP kinase-related pathways</td>
<td>Arborizing polyps; Small intestine &gt; colon &gt; stomach; colonic adenocarcinoma</td>
<td>Pigmented macules; risk of color, breast, lung, pancreatic, and thyroid cancer</td>
</tr>
<tr>
<td>Cowden syndrome, Barnayan-Ruvalca-Biley syndrome</td>
<td>&lt;15</td>
<td>PTEN, PI3K/PKT pathway</td>
<td>Hamartomatous/ inflammatory intestinal polyps, lipomas, ganglioneuromas</td>
<td>Benign skin tumors, benign and malignant thyroid and breast lesions; no increase in GI cancers</td>
</tr>
<tr>
<td>Cronkhite-Canada syndrome</td>
<td>&gt;50</td>
<td>Unknown cause</td>
<td>Hamartomatous polyps of stomach, small intestine colonic; abnormalities in nonpolyoid mucosa</td>
<td>Nail atresia, hair loss, abnormal skin pigmentation, coarctation, and enemas. Fatal in up to 50%.</td>
</tr>
</tbody>
</table>

They all look alike histologically

**Juvenile polyposis syndrome**: SMAD4 mutation.

**Juvenile polyps**: no gene mutation.

**Peutz-Jeghers Syndrome**: STK11, if it’s not a syndrome then there’s no mutation.

Cowden syndrome and Cronkhite-canada syndrome both give Hamartomatous polyps but with different presentation

Cowden syndrome: benign skin lesions like Lipoma.
Cronkhite-canada syndrome (no mutation): diarrhea, hair loss and nail atrophy

Extraintestinal malignancies: thyroid cancer, breast cancer and pancreas cancer.

- **Adenomas:**

  colonic adenomas are precursors to the majority of colorectal adenocarcinomas. But the majority of adenomas do not progress to become adenocarcinomas.

  characterized by the presence of epithelial dysplasia.

  Adenomas can be classified as **tubular**, tubulovillous, or villous based on their architecture. These categories, however, have little clinical significance in isolation. **Size is the most important characteristic that correlates with risk of malignancy.**

  Most adenomas are clinically silent, with the exception of large polyps that produce occult bleeding and anemia and rare villous adenomas that cause hypoproteinemic hypokalemia by secreting large amounts of protein and potassium.

  Adenoma: dysplastic polyp, most common in colon

  polyp : Tubular

  Villous: villi on the surface, tubulovillous: villi and crypts

  Degree of dysplasia: local or high rate

- **Familial adenomatous polyposis** (FAP):

  is an autosomal dominant disorder in which patients develop numerous colorectal adenomas as teenagers.
At least 100 polyps are necessary for a diagnosis of classic FAP, but as many as several thousand may be present.

caused by mutations of the adenomatous polyposis coli (APC) gene. 75% of cases are inherited, while the remaining appear to be caused by de novo mutations.

**Colorectal adenocarcinoma develops in 100% of untreated FAP patients, often before age 30 and nearly always by age 50. As a result, prophylactic colectomy is the standard therapy for individuals carrying APC mutations.**

Not Hamartomatous polyps but multiple adenomas

Mutation in tumor suppressor gene APC chromosome 5

- **Hereditary non-polyposis colorectal cancer (HNPCC):**

Lynch syndrome

HNPCC is caused by inherited mutations in genes that encode proteins responsible for the detection, excision, and repair of errors that occur during DNA replication.

Not a lot of polyps

Family history of colon cancer, mainly the right side

Microscopically indications helps to diagnose mutations in DNA MSH and MLH not the same as in FAP

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Molecular Defect</th>
<th>Target Gene(s)</th>
<th>Transmission</th>
<th>Predominant Site(s)</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familiar adenomatous polyposis</td>
<td>APC/WNT pathway</td>
<td>APC</td>
<td>Autosomal</td>
<td>None</td>
<td>Tubular, villous; typical adenocarcinoma</td>
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On the long term FAP syndrome will become conventional adenocarcinoma

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**Adenocarcinoma**

- Adenocarcinoma of the colon is the most common malignancy of the GI tract and is a major cause of morbidity and mortality worldwide.

- In contrast, the small intestine, which accounts for 75% of the overall length of the GI tract, is an uncommon site for benign and malignant tumors.

- Colorectal cancer incidence peaks at 60 to 70 years of age.

- The dietary factors most closely associated with increased rates of colorectal cancer are low intake of unabsorbable vegetable fiber and high intake of refined carbohydrates and fat. It is theorized that reduced fiber content leads to decreased stool bulk and altered composition of the intestinal microbiota. This change may increase synthesis of potentially toxic oxidative by-products of bacterial metabolism, which would be expected to remain in contact with the colonic mucosa for longer periods of time as a result of reduced stool bulk. High fat intake also enhances hepatic synthesis of cholesterol and bile acids, which can be converted into carcinogens by intestinal bacteria.

- **aspirin or other NSAIDs have a protective effect.**

Diet high in lipid and low in fiber leads to colorectal cancer
NSAIDs will lead to less chances of colorectal cancer

- **Pathogenesis:**

At least two genetic pathways have been described:

- **APC/β-catenin pathway**, which is activated in the classic adenoma-carcinoma sequence. accounts for up to 80% of sporadic colon tumors.

- **microsatellite instability pathway**, which is associated with defects in DNA mismatch repair and accumulation of mutations in microsatellite repeat regions of the genome.

Colonic cancer: because of environmental(diet) as well as genetic, APC and mismatch repair (same in FAP and HNPCC).

If a patient has a mutation in APC, mismatch repair sporadically (without family history, no genetic component for the disease) → sporadic colonic cancer (ex: 60 years old)

If the patient had familial disorders, younger presentation (ex: 20 years old) → FAP or HNPCC (genetic)

When to call it a syndrome? depending on the number of polyps, right side colon with mucinous features in lynch syndrome.
The image represents colon cancer: first APC mutation in addition to mutations in oncogene like K-RAS then conventional adenoma then invasive carcinoma \ invasive cell carcinoma

Microsatellite or DNA mismatch repair defect
APC mutation is more common than mismatch repair defect

- Clinical Features:

Cecal and other right-sided colon cancers are most often called to clinical attention by the appearance of fatigue and weakness due to iron deficiency anemia—iron deficiency anemia in an older man or postmenopausal woman is GI cancer until proven otherwise.

Left-sided colorectal adenocarcinomas may produce occult bleeding, changes in bowel habits, or cramping and left lower quadrant discomfort.

Left-side: sigmoid and descending colon, presentation more than right, why?

right side: the diameter of cecum is more than left

The presentation of left sided is abdominal pain and constipation

Right side: iron deficiency anemia

A student asked if the iron anemia is due to bleeding or malabsorption, the doctor said: minor bleeding in lower GI on long term

- the two most important prognostic factors are depth of invasion and the presence of lymph node metastases—stage

- the liver is the most common site of metastatic lesions. The rectum does not drain via the portal circulation, hence carcinomas of the anal region that metastasize often circumvent the liver.
If a patient asks how long does he have left to live: it depends on the stage, is it in mucosa, submucosa, or outside the colon?

We determine the stage pathologically by testing a sample from the colon or by radiology to the whole body.

Early stage means better survival rate.

- Tumors of the Anal Canal:

Carcinomas of the anal canal may have typical glandular or squamous patterns of differentiation, recapitulating the normal epithelium of the upper and lower thirds, respectively.

Same as colon cancer

Squamous epithelial lining in the lower part of anal canal we will find squamous cells there.

Appendix

- Acute appendicitis: is most common in children and adolescents. It is thought to be initiated by increased intraluminal pressure and compromised venous outflow, usually caused by a small stone-like mass of stool, or fecalith, or, less commonly, a gallstone, tumor, or mass of worms (oxyuriasis vermicularis).

Typically, early acute appendicitis produces periumbilical pain that ultimately localizes to the right lower quadrant, followed by nausea, vomiting, low-grade fever, and a mildly elevated peripheral white cell count.
A classic physical finding is the **McBurney sign**, deep tenderness located two thirds of the distance from the umbilicus to the right anterior superior iliac spine (McBurney point).

Inflammation of appendix: obstruction by material like food particles and worms

- **Tumors of the Appendix:**

  The most common tumor of the appendix is the welldifferentiated neuroendocrine (carcinoid) tumor. It is usually discovered incidentally at the time of surgery or examination of a resected appendix.

- Other tumors:
  - Conventional adenomas
  - non–mucin-producing adenocarcinomas
  - Mucinous cystadenoma
  - mucinous cystadenocarcinoma— pseudomyxoma peritonei