

3.10.2021

3rd Lecture

Pathology of GIT

Achalasia

Characterized by 3 things:

- 1- aperistaltism → loss of peristaltic movement
- 2- Increased lower sphincter tone
- 3- Failure to relax during swallow (shinder relaxation)

Lead to functional esophageal obstruction

↳ with time → dilatation → accumulation of some food inside the esophagus → regurgitation → Aspiration (enters respiratory tract)

* to be sure of diagnosis → measuring pressure in different parts of esophagus

Has 2 Problems:

- ① Loss of ganglion cells (which are responsible of peristaltic m.)
↳ responsible for moving smooth muscle layers.
- ② Failure of relaxation of lower sphincter (esophageal)
related to Nitric oxide transmitters (neurons) → failure

Destruction of ganglion cells:

If there is a clear reason → 'secondary'

If there is no clear reason → 'primary' → rare and results from degeneration of nitric oxide-producing neurons

Absence of ganglia and sequencing process → inflammatory process

Result: Increased risk for esophageal squamous cell carcinoma (5%)

⇒ Destruction of ganglia due Chagas disease (*Trypanosoma cruzi*) → Secondary achalasia

causes

↳ Destruction of myenteric plexus or ganglion cells → may also have other reasons:

- Diabetic immunopathy
- infiltrative disorders as C.T diseases
- Tumors, malignancy, (amyloidosis, sarcoidosis, systemic sclerosis)
- Down syndrome → Lower esophageal sphincter dysfunction or Algrove syndrome

Treatments

- Myotomy (surgical) (laparoscopic myotomy) + Botox injection
- Balloondilatation (Levin)

Mallory weiss syndrome: longitudinal tears in mucosal layer of the lower part of the esophagus

→ Normal peristalsis from mouth to anus, but sometimes while vomiting we have the opposite → contractions from proximal to distal.

Alcoholism
people getting chemotherapy } failure in contraction and relaxation
while vomiting → high pressure → star
↓
Bleeding

↳ Mallory weiss syndrome → 10% of upper GIT bleeding.

Complication: tear in mucosa → can reach muscle layer
↳ rupture

⇒ **Boerhaave syndrome**
contents of digestive system enter
mediastinum → high mortality
due to mediastitis

Esophagitis: Inflammation of Esophagus.

Triggering factors:

- Nasogastric tube after long usage
- Uremia & Boli disease → ingestion of corrosives
- Estrogenic → radiation therapy
- Virus → Herpes S.V
- Immunosuppressed persons → Cytomegalovirus

Virus replication → summation → inclusion body (nuclear)
in nucleus

Candidiasis Infection → In newborns
and immunocompromised

↓ white membrane
hyphae (fungus)
inflammation

Reflux Esophagitis

↳ Returning of materials in stomach to lower part
of esophagus

Also called : Gastro-Esophageal - Reflux - Disease GERD

Pathogenesis

Normally Esophagus to stomach (a defect happens):

- ⇒ Transient lower esophageal sphincter relaxation is
thought to be the major cause.
- ⇒ Sliding Hernia → Gastroesophageal junction with part
of stomach → back to thorax cavity
- ⇒ Enlargement of stomach size → after lots of food
- ⇒ Defect in reparative mechanism of epithelium

Morphologically:

- ① - appearance of neutrophil leukocytes
- ② - Basal zone hyperplasia: more than one single layer (proliferation)
- ③ Elongation of Lamina Propria: between epithelium & sub-epithelium

Clinically

- Heartburn: pain at stomach is caused by pinching of oesophagus
- Complications and inflammation, Bleeding
- narrowing of lower sphincter due to fibrosis

Bowel esophagus: Replacement of squamous epithelium by intestinal type epithelium (contain Goblet cells)

→ Fertile soil of cancer

Eosinophilic Esophagitis

↳ found also in colon etc...

⇒ found in "atopic persons": hypersensitivity (skin rash, food allergy)



Eosinophils high

IGE High

Microscopically:

- In Reflux: Scattered eosinophils (one or two)

⇒ sheets of eosinophils in Eosinophilic Esophagitis. (Cells)

Treatment

Steroids

Esophageal varices

⇒ At points where the portal system & systemic circulation meet (as lower esophagus, and lower rectum, near umbilicus)

Sometimes a defect happens here due Thrombus or Liver disease

↳ expansion of these vascular structures ⇒ Erosion

↳ Serious bleeding

Microscopically:

Thrombosed bleeding

Barrett esophagus:

The place where dysplastic changes begin to happen

→ Adenocarcinoma

Note: Patients with lower esophageal carcinoma are most of the time pre-diagnosed with Barrett Esophagus. But not every case with Barrett Esophagus will turn into cancer.

4:1

due to esophageal reflux frequently

Male: Female

Morphologically:

- Intestinal type of Mucosa

- Columnar cells

- Goblet cells → most diagnostic

- 3" → short segment, 3" → long segment

- maybe asymptomatic or connected with "gastric" symptoms

→ tongue-like extension,

- Obesity
- Smoking
- Radiation

} Risk factors for Barrett

most common
cancer in USA

Esophageal carcinoma:

Squamous cell carcinoma

Adenocarcinoma

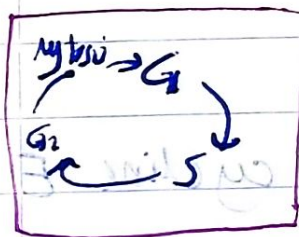
- H. Pylori after long time $\rightarrow$ atrophy
- Obesity-related gastroesophageal reflux and associated Barrett

Pathogenesis

TP53 $\rightarrow$ guardian of genome (detects defects)

CDKN2A ~~is~~ control of cell cycle: cycline dependent
kinases
 $\hookrightarrow$ from P16

cycline dependent $\rightarrow$ stops work of kinases
kinase inhibitor



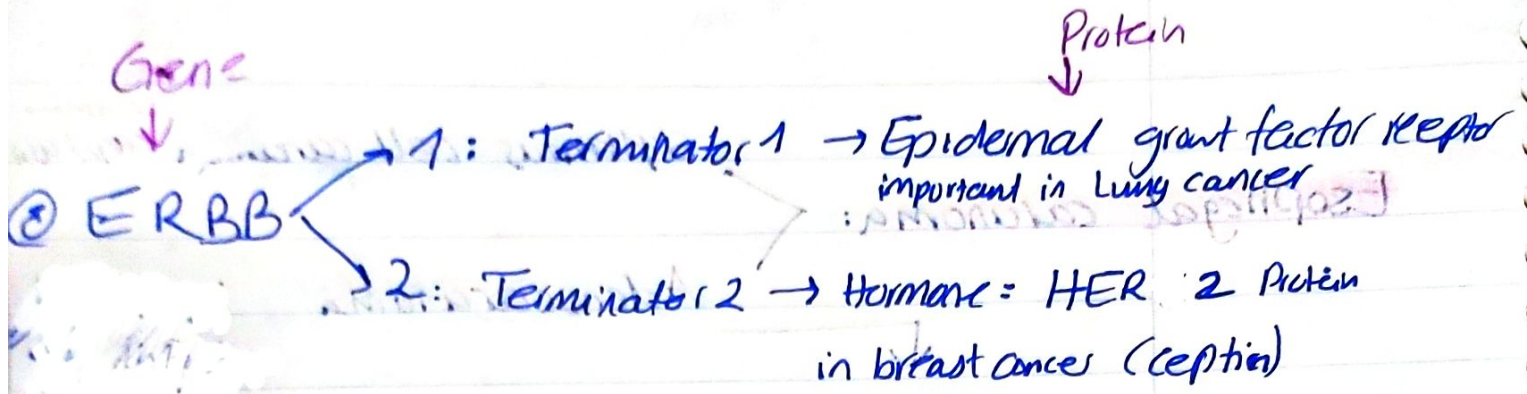
Two checkpoints: $G_1 \rightarrow S$ $G \rightarrow$ lysos

$\Rightarrow$ Progression

① EGFR. Epidermal growth Factor

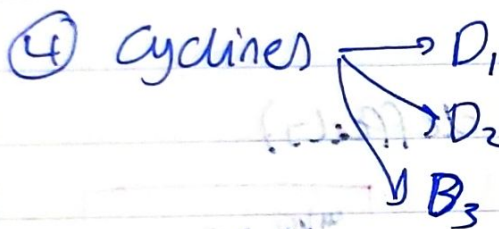
- see second lecture page 2 -

$\hookrightarrow$ G-Dependent kinases and inhibitors control that cycle



α receptor $\rightarrow$ membrane, GF $\rightarrow$ from outside α

③ MET: transcription factor (mostly 3 letters)



⑤ cyclin E

Clinical features

- increase in size
- dysphagia

Prognosis $\rightarrow$ bad (if not discovered early)

Squamous cell carcinoma

Age 54+, related to lifestyle

risk factors: alcohol tobacco, (poverty)⁺, hot drinks, radiation

achalasia → Plummer Wilson syndrome

Iran, China, Kenya ⇒ food style

- fungal contamination

- HPV

⇒ To become a cancer

① Limited renewal potential (انقسام محدود)

② (Stepwise) Invasion ability

③ Metastasis and making a mass

④ overexpression of cyclins

* Protein oncogenes → in normal cells → mutation happens

↳ advantage to home

Oncogene

* Tumor suppressor genes → opposite to oncogenes as TP53, CDH1, NOTCH1

CDH1: encodes E-cadherin

↳ bounding of cells

↳ if lost: no bounding, fall apart → pro-cancerogenic

→ certain jobs

* Squamous cell carcinoma is predisposed with dysplastic changes → but hard to detect (nuclear changes).

* Esophageal cancer is rich in lymphatic and blood supply

* not lined by serosa → fast spread

* most worse: Esophagus cancer

second worse: Stomach cancer

less worse: Colon cancer

* anatomically:

- lower third lymphatic drainage: around stomach, upper abdomen

- middle third " " : mediastinum lymph nodes

- upper third " " : cervical area

important to know where
it's going to spread

Spread → Circumferential: around the area

longitudinal: due / via vessels & lymphatics
in esophagus

nucleomorphism: changes in shape, some large / small

STOMACH

Definitions:

Gastritis

↳ Neutrophil leukocytes in epithelium (infection)

Gastropathy: no neutrophils, other changes
chemical factors, alcohol
bile regurgitation

Protective agents: Pepsin, HCl, mucus, Bicarbonate
well developed blood supply, high regenerative capacity

↓ defected (as O₂ delivery)
Problem

⇒ drugs as non steroidal anti-inflammatory drugs,
and alcohol → direct impact

Acute

short termed
neutrophils

Chronic

long termed

lymphocytes, plasma cells & normally

— exceptions in histology —

↓
active — chronic inflammation

Stress-related mucosal disease

↳ Physiologic stress

↳ Ulcer in stomach

① Stress ulcers: no specific place in stomach

↳ after shock, sepsis or severe trauma

② Curling ulcer: after burns, at proximal duodenum

③ Cushing ulcer: due to central nervous system diseases

↳ in brain (intracranial)

↳ Perforation risk

compared to peptic ulcers: Stress-ulcers happen in a short time

ulceration: loss of tissue/mucosa

- base lined by inflammatory cells

- no fibrosis as peptic ulcer (chronic)

↳ gets well after a week commonly

Pathogenesis: most often related to local ischaemia

(due systemic hypotension or reduced blood flow)



active inflammation

Clinically → gastric mucosal damage → bleeding

Causes of gastric bleeding =

① Dieulafoy lesion

submucosal arteriole → gastric bleeding

② Gastric antral vascular ectasia (GAVE)

Chronic gastritis

most often caused by *H. Pylori* infection, (autoimmune gastritis 10-20%, mechanical injury due to nasogastric tube, or involvement by other systemic diseases)

H. Pylori Gastritis

- In some researchers 80%

→ likes pyloric antrum of gastric area & increased acid production

- Transmission: oral-fecal

- In poorer countries ↑, rich countries ↓

- Chronic gastritis → continuous inflammation → atrophy in mucosa

↓
intestinal metaplasia → ↓ Parietal & chief cells

For differentiation:

(Atrophic)

(Ch. pylori infection)

Autoimmune gastritis: - gastrin $\uparrow$, problem in fundus & body

- parietal cells nearly not found

$\rightarrow$ achlorhydria (no acid at all)

Histologically:

Glands $\rightarrow$ replaced by ^{lymphatic} and plasma cells

Microorganism: - many microorganisms that help in being

viral microorganisms:

- **Flagella** for movement

- **Urease Enzyme**: urea from ammonia

$\rightarrow$ lowers acidity, $\text{pH} \uparrow$

- **adhesins**: factors that secure binding of cells

- **Toxins**: cytotoxin associated gene A (Cag A)

important in pathogenesis due that they

colonize gastric body and induce proinflammatory cytokine secretion

Prevalance: all current cases

incidence: cases in a specific time (mostly a year)

atrophy
 $\downarrow$
intestinal metaplasia

* long period of inflammation may cause cancer

* *H. pylori* related to Adenocarcinoma and Lymphoma

$\rightarrow$ neutrophils very visible

Metaplastic atrophic gastritis where etiology is H. Pylori or Autoimmune → visible

Autoimmune gastritis

- as previously said, spares the Antrum (قاع)
- reaction against intrinsic factors and parietal cells
- also destruction to chief cells while inflammation

↳ pepsinogen producer

↳ Stimulus to G-cells (Gastrin inducing)

↳ increase of size → nodule (visible)

⇒ B12 deficiency:

① Megaloblastic anemia (also due folate acid deficiency)

→ large size of cells → pernicious anemia

② affects nervous system

- achlorhydria → most of parietal cells are destroyed (diffuse)

↳ but H. Pylori → Patchy

Table 17.2 Characteristics of *Helicobacter pylori*-Associated and Autoimmune Gastritis

	<i>H. pylori</i> -Associated	Autoimmune
Location	Antrum	Body
Inflammatory infiltrate	Neutrophils, subepithelial plasma cells	Lymphocytes, macrophages
Acid production	Increased to slightly decreased	Decreased
Gastrin secretion	Normal to increased	Increased to markedly increased
Other lesions	Hyperplastic/inflammatory polyps	Neuroendocrine hyperplasia
Serology	Antibodies to <i>H. pylori</i>	Antibodies to parietal cells (H ⁺ K ⁺ -ATPase, intrinsic factor)
Sequelae	Peptic ulcer, adenocarcinoma, MALToma	Atrophy, pernicious anemia, adenocarcinoma, carcinoid tumor
Associations	Low socioeconomic status, poverty, residence in rural areas	Autoimmune disease: thyroiditis, diabetes mellitus, Graves disease

H⁺K⁺ ATPase, Hydrogen potassium adenosine triphosphatase; MALToma, mucosa-associated lymphoid tissue lymphoma.

Uncommon forms of Gastritis

1 - Eosinophilic Gastritis

2 - Lymphatic Gastritis

3 - Granulomatous Gastritis

Peptic Ulcer Disease

→ Fibrosis, thickening → old

⇒ Chronic mucosal ulceration affecting duodenum & acidic stomach

either ↑ acid
production/
secretion

defect in protective / defense
mechanism

Atrophy → Metaplasia → Cancer

H. Pylori → Loss of parietal cell → ↑ pH

Peptic ulcer

⇒ non steroidal anti-inflammatory, smoking are risk factors
+ ectopic gastric mucosa (Meckel's diverticulum)

Pathogenesis

imbalances between defense mechanisms & damaging factors
that cause chronic gastritis (long term)

Morphologically:

> 80% → flat, round to oval ^{الاجزائ}
" Sharpley punched-out defect "

but in cancer ulceration:
" heaped-up "

Place:

→ commonly first part of duodenum and in stomach
point of connection between antrum and corpus.