

10.10.2021

4th Lecture

Pathology - GIT

Hypertrophic Gastropathies

Hypertrophy: increase in size

Hyperplasia: increase in number of cells

↳ They are uncommon diseases

→ due epithelial hyperplasia (initially it was falsely thought to be hypertrophy)

→ without inflammation

→ increased growth factors (hyperplasia, mitosis)

Examples for hypertrophic Gastropathies: (rare)

Ménétrier Disease

- associated with secretion of transforming growth factor α
- increased risk of adenocarcinoma

Treatment

- G.F. blockers may be useful

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TIP - pathology

Microscopically:

- Complex architecture
- $\bar{E}P$ in surface epithelium $\rightarrow$ hyperplasia
- Tubular glands decrease in number
- hypoproteinemia due to albumin loss

Zollinger-Ellison Syndrome

Background:

Diffuse neuroendocrine system $\rightarrow$ neuroendocrine cells

$\rightarrow$ secrete mediators that organize the work of GI system

Gastrin $\rightarrow$ stimulation of parietal cell $\rightarrow$ acids $\uparrow$, enteric factors $\uparrow$

$\Rightarrow$ Pathogenesis:

Benign ^{neuroendocrine} tumor (usually) found along the GI tract that secretes large amount of gastrin leading to many ulcers

- almost always found in small intestine or Pancreas

Gastric Polyps and Tumors

⇒ There are a sum of polyps that affect the stomach.

A polyp is a protrusion - finger like projection from organs that have space.

There are 3 Types of polyps

- ① Inflammatory and hyperplastic polyps
 - ↳ due to increase in amount of cells
 - the most common type → in 75% of cases
 - H. Pylori infection - 50-60 years
 - no association with cancer normally, but when found in stomach there's 1:20 risk of dysplastic changes and then cancer formation
 - ~~foveolar~~ epithelium or gastric bed's is the entrance of glands - neck, isthmus, then branches into 2-3 tubules

↓
gastric glands

organized shape, tubelike structure

→ due to increase in number of cells → angular

↓
convolution

② Fundic gland polyp

- PPI got widely and often used through the past years (falsely)

↓ Acid ↓ → Gastrin ↑ → Stimulation of parietal cells → Poly P formation (benign tumor)

- no risk of cancer
- **APC gene** → germline mutations (the cause of familial adenomatous polyposis)
- **MUTLH gene** (DNA repair gene)

In Both a defect happens → fundic gland

Microscopically:

- Bright Eosinophilic (red)
- dilated gland
- Chief cells, mucus secreting cells, parietal cells ↑↑↑

③ Gastric Adenoma (also a polyp)

Most gastric adenomas develop in background of chronic gastritis with atrophy and intestinal metaplasia (dysplastic changes after that → mass (gastric adenoma))

- 10% of polyps that present in stomach
- frequency increases progressively with age

^{risk for}
Side Note: Cancer increases with age due to affection
: of more carcinogens

- males affected 3 times more often than females
- Gastric adenomas have a greater risk of cancer (up to 30%)
- Size of tumor plays an important role

Gastric Adenocarcinoma

↳ most common malignancy of the stomach
(comprising more than 90% of all gastric cancers)

Adenocarcinoma
 → intestinal type (forms bulky masses)
 → diffuse type (infiltrates & thickens gastric wall)

- The stomach has a wide lumen (space inside)

↳ symptoms of cancer won't be seen early and only at late stages

Epidemiology

- In USA 100 years ago → death cause No. 1

↳ Now: 2-3% of mortality of cancer

USA, Europe → H. pylori different than poorer countries

- Japan, Chile, Costa Rica & Eastern Europe:

↳ 20 fold higher than other countries

- A study on Japanese immigrants in USA showed:

1st Generation: 20% (as homeland)

Other Generations: percentage decreases

↳ related to environment

Most common involved sites:

- Left supraclavicular lymph node (Virchow node)

- Periumbilical lymph node (Sister Mary Joseph nodule)

- Ovaries (Krukenberg) usually bilateral

- left axillary node

- pouch of Douglas (pouch between rectum & vagina)

↳ lowest point in peritoneum

- Increased socio economic status → reduced rates of H. Pylori infection and less intestinal cancer (relates to it)

↳ Excluded here: cardia of stomach (gastric cardia ↑)
↳ probably related to Barrett esophagus, GERD & Obesity.
(Gastric cardia & esophageal adenocarcinomas are similar in morphology)

To diffuse type:

- characterized by diffusion in stomach
 - ↳ no well defined mass seen usually
 - ↳ infiltration in wall, rugae
 - ↳ thickening of mucosa
 - ↳ desmoplastic (Connective Tissue) reaction
 - ↳ hardness, stiffness, thickening.
- linitis Plastica → diffuse type (latter bottle)

Pathogenesis:

E-cadherine: Promotes connection between cells

↳ encoded by **CDH-1** gene

↳ in diffuse type: mutation here
(cells appear single)

↓
- happens also in breast cancer
⇒ "invasive lobular carcinoma of breast"
↳ extensive despositiveness of tumor cells

In diffuse gastric cancer:

Mutation in ordering of nucleotides $\rightarrow$ genetic disorder

Mutation/defect in proteins of nucleotides/DNA $\rightarrow$ epigenetic disorder

CDH1: sometimes genetic or epigenetic

50% - 50%

In intestinal gastric cancer

related to:

* APC $\rightarrow$ adenomatous polyposis coli

- IG cancers are strongly associated with mutation that results in increased signalling via Wnt pathway

activated by receptor

Proteins

Normally: β -catenin + APC $\Rightarrow$ Ubiquitin

Proteasome: its work is to get rid of unuseful proteins

$\rightarrow$ to work: it needs a signal $\rightarrow$ ubiquitin

Process: Ubiquitination

We have a growth pathway here that leads to division of the cell. Growth factor Wnt binds to receptor, which leads to stop of work of APC $\rightarrow$ β -catenin $\uparrow$

When β -catenin increases $\rightarrow$ translocation to nucleus
 $\rightarrow$ starts a row of actions that lead finally to
division of the cell.

This pathway is the most important in intestinal type
of gastric adenocarcinoma, as well as:

- Tumor suppressive genes
- Transforming growth factor β
 $\rightarrow$ inhibits mytosis $\rightarrow$ against cancer
 - PAX: proapoptotic factor
stimulates apoptosis $\rightarrow$ smth. against cancer
 - CDKN2A (in oral & esophageal also)
 $\rightarrow$ T16: stops work of kinase
cyclin: stimulates
- loss of function
 $\downarrow$
cancer
- بتثقل فيه الكانسر في الامل

Morphologically:

Diffuse types

no well defined mass usually, thick mucosa, prominent vasc.,
intracytoplasmic secretions

Intestinal type:

- mass $\rightarrow$ can be protruding inside lumen $\rightarrow$ can cause
deep perforation $\rightarrow$ obstruction
- secretion in lumen / large nucleus
of adenocarcinoma
(like gland)

In tumors microscopically:

Anatomic destruction & complete loss of anatomic landmarks

formalin → fixing agent

- Lymph node along greater curvature sometimes also invaded with tumors

- large and prominent nucleus in ~~these~~ tumors

In diffuse type:

intracellular secretions, mucus inside cytoplasm → Vacuole

→ Push nucleus inside plasma membrane

Lymphoma

1. T-LIAA 01/10/14

- Extranodal lymphomas can arise in any tissue but they do most commonly in GI Tract, particularly stomach (cancer called MALTomas)
- Immunosuppressive drugs play an important role here, as they lead to lymphoma in the body, with under the GI tract
- 5% of all gastric malignancies are primary lymphomas (5% of the UK)

Pathogenesis:

There are 3 Translocations (t) - (p, q: to show where)
↳ A part of DNA changes place with another

t(11;18)(q21;q21)

the less common t(1;14)(p22;q32)

t(14;18)(q32;q21)

→ These 3 Translocation affect two important genes:

BCL10, MALT1

Those 2 genes stimulate an intranuclear factor called **Nuclear factor Kappa B** → responsible for leading cell into mitosis

Normally, **Lymphocytes** work with the same way:

Antigenic stimulation $\xrightarrow{\text{response}}$ activation of 2 genes

MALT1, BCL10

↓
Expression of genes

↓
survival & proliferation of lymphocyte

↓
(Antigen response) +
(Immune response stimulation)

(Can take a day - month)

* Chronic H. Pylori infection can take "decades" to show symptoms. While this time B & T cells were at a continuous stimulation $\xrightarrow{\text{lead to}}$ mutation, defect → Tumor lymphoma

* If we however cure H. Pylori → no stimulation anymore → Back to normal (which is rare) with antibiotics or tumor progression

* In not H. Pylori related lymphomas; the cause is one of the translocations mentioned earlier
↳ activation of *myc* genes ^{autonomously} → same result

Note
⇒ H. Pylori curing wouldn't change anything in this case.

Tumor progression:

Normally, cells divide when it's time & when they get an order to do so. (from signals)

100 Mutations need to happen in a cell to change it into a cancerous one

^{for example}
The first: in DNA-repair mechanism (في الرقبة يوقف راي)

...
⇒ The replicated cells of this cell are cancerous too
↳ not normal genetic make up → fast division

- Sometimes, from this genetic make up a new "sub-clone" gets created
- ↳ Different genetic structure between the tumors.

Morphologically:

- Stomach mucosa diffusely infiltrated by lymphocytes
- Lymphoepithelial lesion: characteristic

- Tumor in Zollinger-Ellison syndrome

- mediators - Vasoactive amines

↳ affect dilation of blood vessels + bronchospasm

↳ flushing - itchy - crampy pain

Carcinoid

First-pass effect:

From stomach to rectum: Portal vein → Liver

∴ So any tumor in this area would be recognized and treated by liver → no symptoms

Related to aggressiveness:

Stomach & Duodenum → Foregut Endocrine tumor

Jejunum & ileum → Midgut Endocrine tumor

Colon, appendix, rectum → Hindgut Endocrine tumor
neuro

to conclude:

- So, **neuroendocrine Neoplasms**: arise from the diffuse tissue/components of the endocrine system.

- They are well-differentiated.
- 40% occur in Small Intestine
- They may be associated with endocrine cell hyperplasia, autoimmune chronic atrophic gastritis, MEN-1 & Zollinger-Ellison syndrome.

Gastrointestinal Stromal Tumor (GIST)

- We talked that the previously discussed tumors are
 - Gastric adenocarcinoma: epithelial origin
 - Lymphoma: hematocytic system or lymphocytes - epithelial
 - Neuroendocrine - epithelial origin also

Stroma & CT ⇒ can be a source for tumors

- rarely : 10-20 per million
- elderly
- arise from intestinal cajal cells

Pathogenesis:

- KIT (or CD117) mutation in 75% of cases
↳ Cluster Differentiation (1-200)

Morphologically:

- Stromal → spindle cells, build carcinoma.
(elongated cells) → spindle cells
↳ fibrotic areas - (no pleomorphism in nucleus)
- Tumor from muscularis propria
↳ symptoms can rise up when it starts to affect neighbouring organs

but in adenocarcinoma starts from mucosa → ulcer, bleeding etc → earlier symptoms than GIST.

Behavior & Prognosis:

related to 3 things:

- ① Mitotic activity
- ② Size of tumor
- ③ Location of Tumor

Treatment

- ① Surgery
- ② ~~anti~~ imatinib: example for targeted therapy

Immunohistochemical studies: markers or antigens

to differentiate specific parts

المنح: تفاعل كيميائي (المنح: التفاعل)

SMALL INTESTINE & COLON

Intestinal Obstruction

→ SI is very long & important organ → any obstruction would cause serious problem

→ Obstruction is a frequent problem in SI due to its small diameter, usually due to visceral protrusion

- 80% of Intestinal Obstruction cases go back to one of four reasons:

① Hernia: most common cause

↳ Outgo of part of organ from peritoneal cavity to somewhere externally (under skin), as:

inguinal canal - most frequently

to scrotum

narrow orifice → edema & large sacs

↳ bulk of herniated loop

Hernia sac: Protrusion of a serosa-lined pouch of Peritoneum

abdominal & venous compromise and infarction

↑ permanent entrapment

Adhesion

After Surgical procedures (operations), inflammation, infection or endometriosis → repair mechanism

↳ Bands of CT between bowel segments, the abdominal wall or operative sites

↳ making internal herniation; where a part of the bowel gets stuck (between bands)

↳ Obstruction & Strangulation (similar to external)

Volvulus

↳ occurs when a loop of bowel twists about its mesenteric point of attachment resulting in



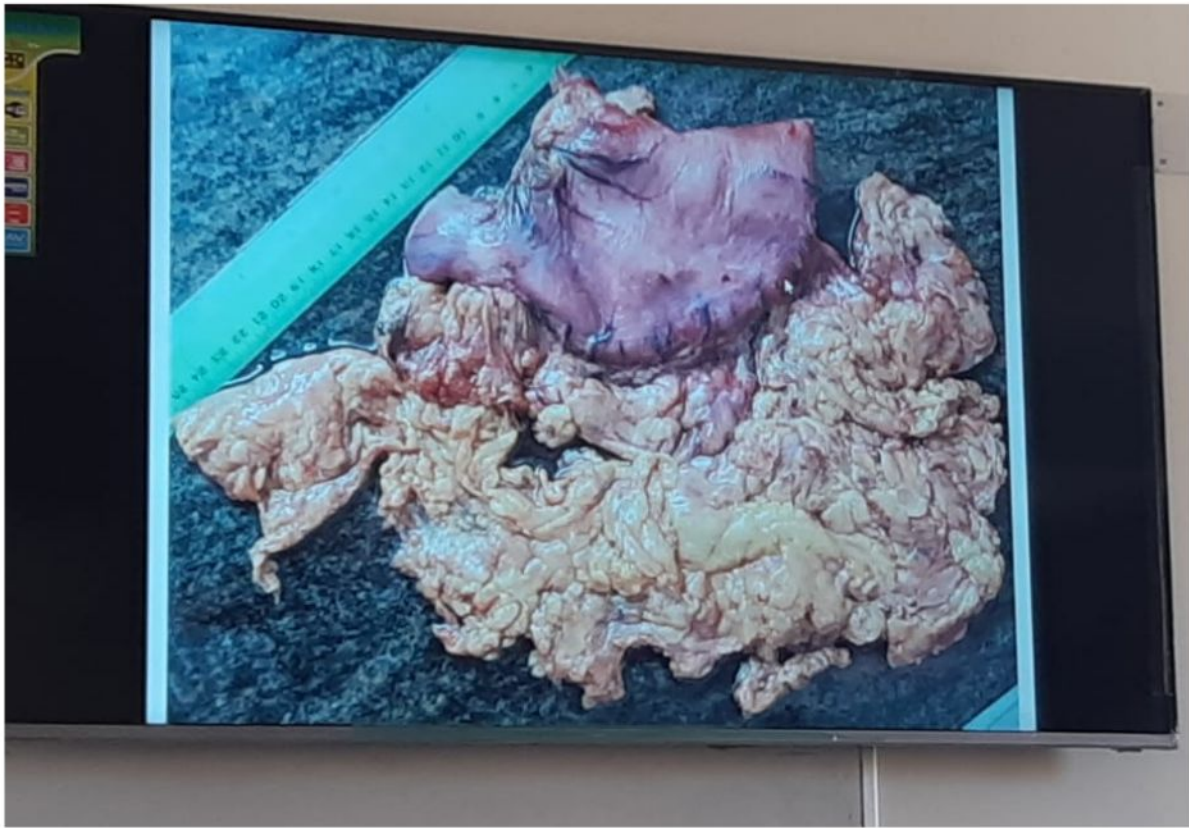
luminal
compromise

vascular
compromise
regions

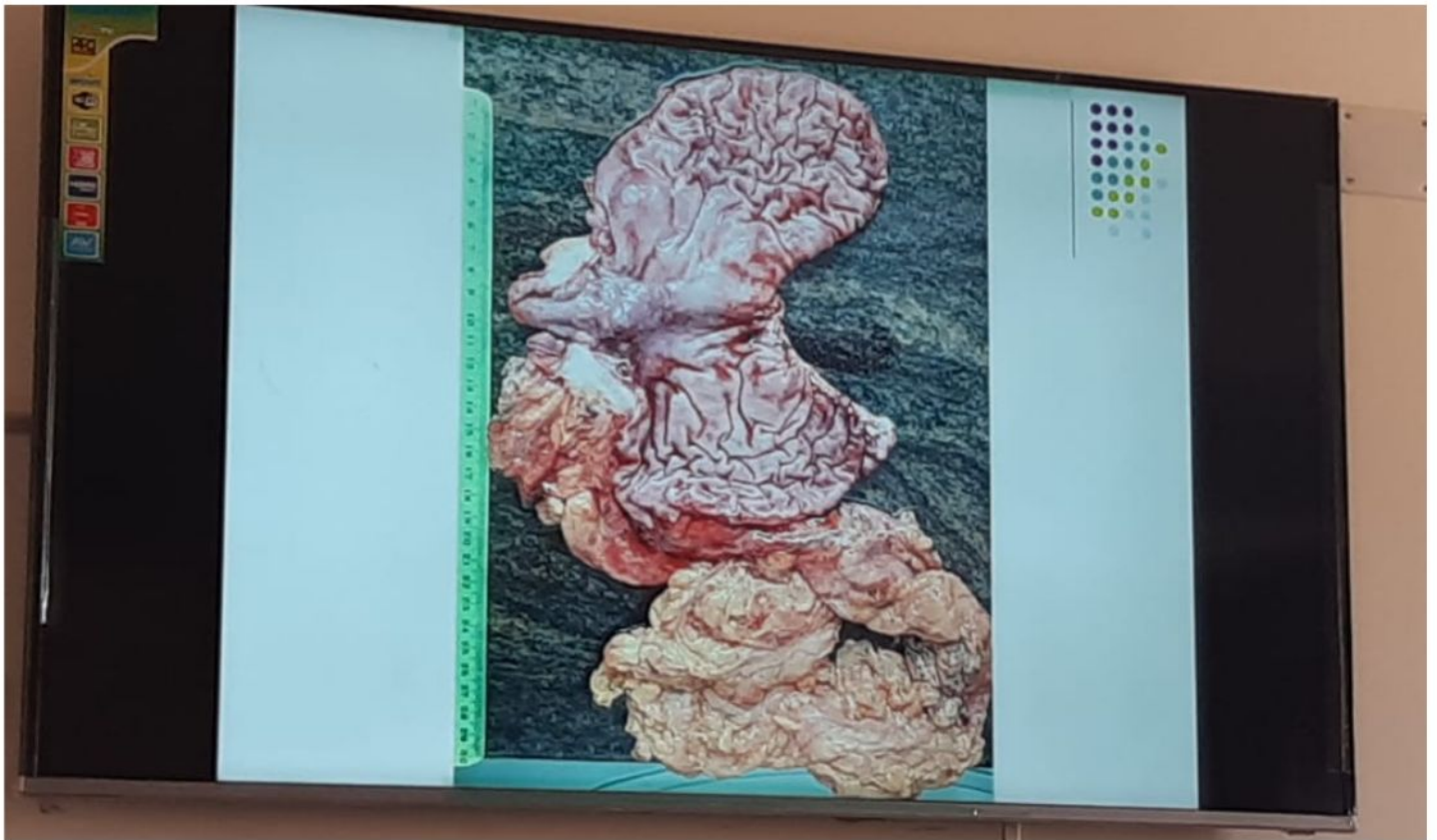
- Most common in sigmoid colon (and patients with enlarged sigmoid colons) followed by cecum & SI

- because it is rare, can be overlooked and forgotten

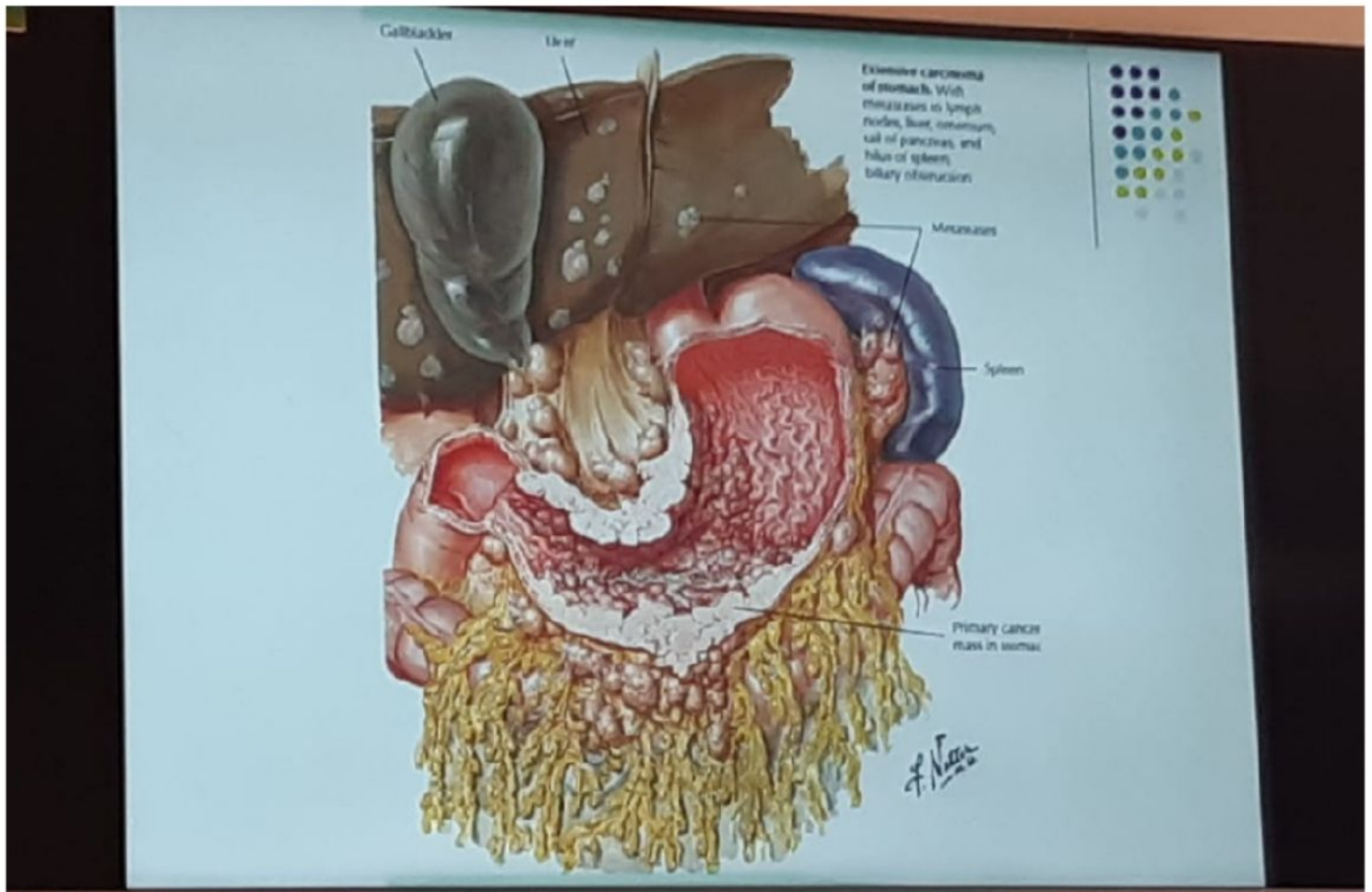
Abeba Edwan



Partial gastrectomy (body and fundus remained in patient)
The fatty yellow part: greater omentum

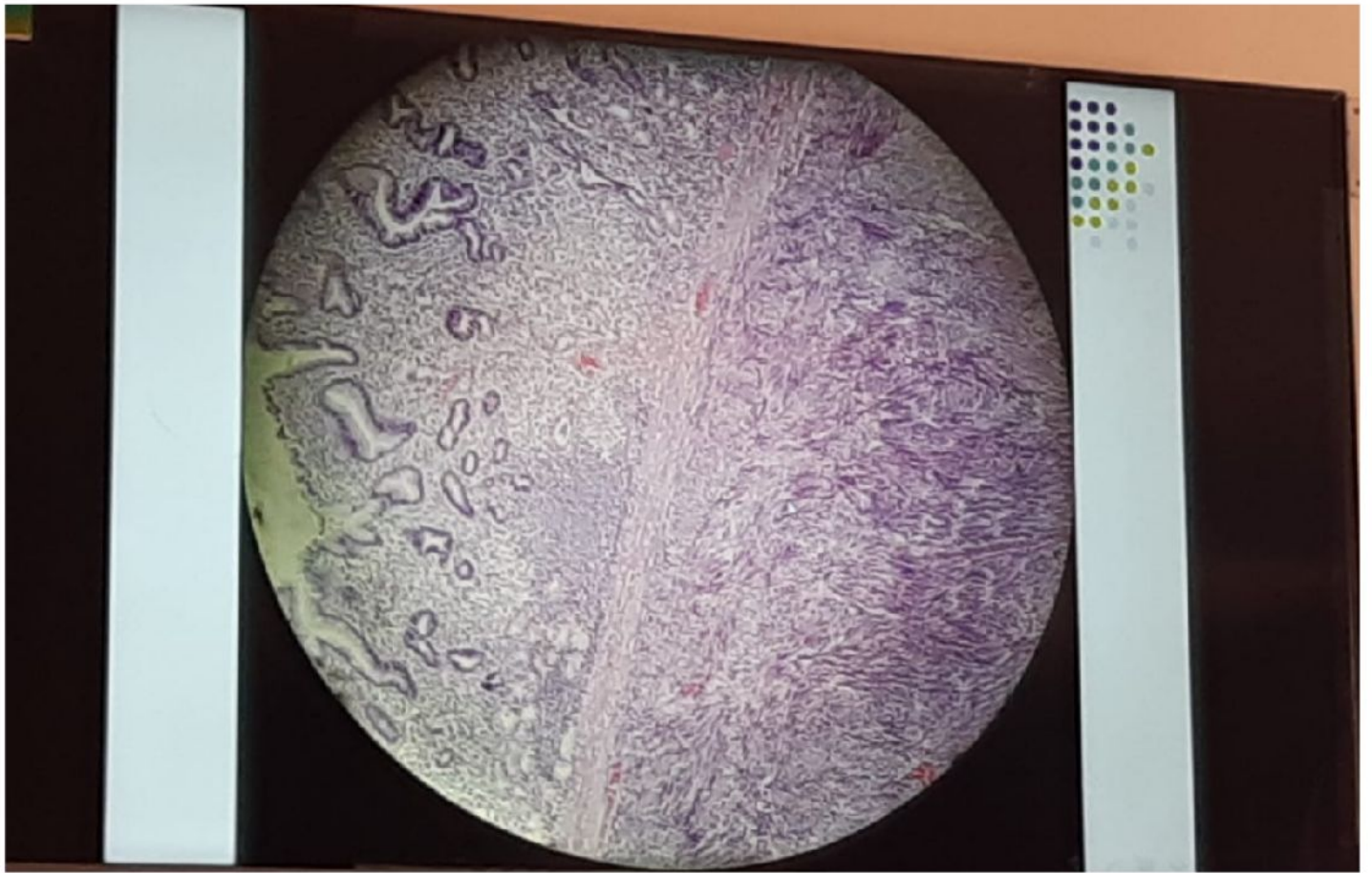


- opened/incision from greater curvature (butterfly appearance)
- The white on the left: Sphincter
- smooth muscle cells well defined and prominent in pylorus area
- There's also an ulceration (loss of tissue)
 - surrounding of ulcer is thickened, rigid
 - rugae disappears around ulcer - flattening



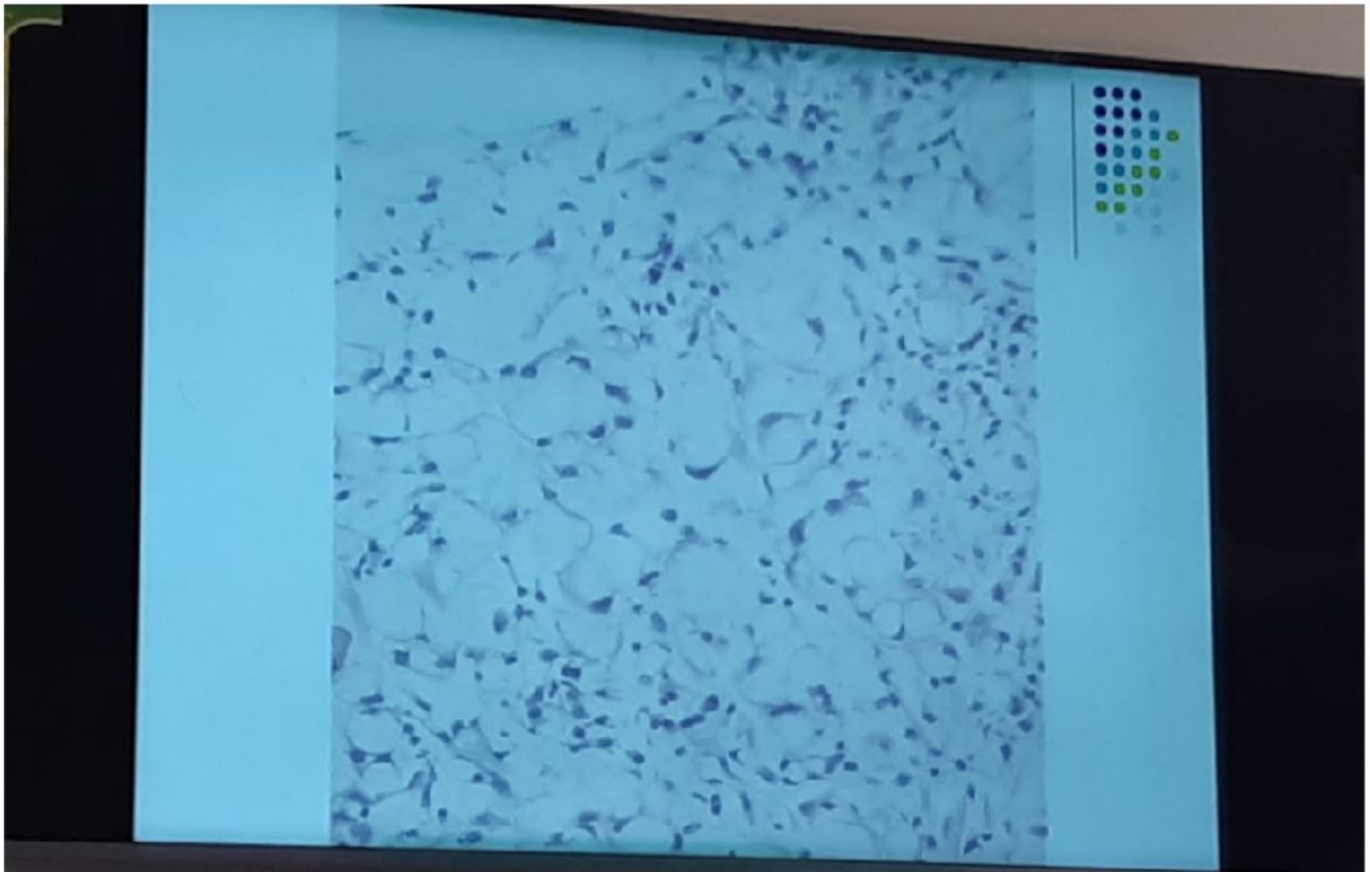
Coronary section showing characteristics of an advanced tumor:

- Lymph nodes along greater curvature are invaded by tumor and there are even tumors on the greater omentum
- Lymph nodes of lesser curvature also invaded
- Hilum of spleen and lower surface of liver are also invaded



Intestinal type of gastric adenocarcinoma (H&E stain):

- irregular cells that build a "lumen" (that's why it's named adenocarcinoma)
- That lumen has secretions inside (pale)
- Large nuclei and prominent nucleolus



Diffuse type of gastric adenocarcinoma:

- Characterized by intracytoplasmic cells that secrete mucin
- mucin (clear) stays inside cytoplasm forming a vacuole that pushes the nucleus to the membrane
- these cells are called "signet ring cells" -> signet ring cell adenocarcinoma



حالات برضو

