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Review

What is gastritis? What is gastropathy? How is it classified?

STOMACH

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ABSTRACT

Stomach endoscopic biopsies are made to determine the diagnosis of the illness, its stage, and follow-up after the treatment. It is very significant to collaborate with the clinician while evaluating endoscopic biopsies. Besides the clinical and laboratory information of the patient, the endoscopic appearance of the lesion should be known. The clinician and pathologist should use the same language and the same terminology. Although new classifications have been made to prevent the confusion of terminologies in neoplastic processes recently, most centers around the world have reported non-invasive neoplasias without giving any certain diagnosis by just commenting on it. The clinician should understand what the pathologist wants to say; pathologists should know the approach of the clinician (repetition of the biopsy, endoscopic resection, surgery). There is Helicobacter pylori (HP) in most of the stomach pathologies as the etiologic agent. No matter if the factor is HP or other etiologic agents, the tissue gives similar responses. That is why clinical-endoscopic indications should be taken into consideration, as well as histological indications, and the reports of the endoscopy should be seen. A good clinicopathologic correlation increases the accuracy of the diagnosis.

Keywords: Gastritis, gastropathy, classification

Gastritis is an infectious or auto-immunological inflammation. Gastropathy can be described as a pathology that displays epithelial injury and regeneration, and it is secondary to endogenous or exogenous irritants.

In practice, "gastritis" may be accompanied by mucosal injury, while "gastropathy" may show, even if minimal, an inflammatory reaction.

CLASSIFICATION

There is no universal categorization of gastritis and gastropathy, but they can be categorized according to their duration of development (according to the inflammation type) and acute/chronic etiology.

GASTRITIS

Gastritis is an inflammatory condition of gastric mucosa that displays changes related to etiology and the host response. It was identified in the 1800s as a result of autopsies. There may be similar morphological images of gastritis based on different etiologies, and there may be more than one etiologic agent in a gastritis chart.

Gastritis was categorized as chronic and acute in 1947 for the first time. Then, chronic gastritis was categorized into two subgroups: namely, superficial and atrophic.

After Marshall and Warren demonstrated in 1983 that a bacteria called Campylobacter pylori caused gastritis, a tendency of an etiology-oriented denotation began. For this purpose, a group of gastropathologists prepared a classification in 1990 in Sydney for the first time to classify and rank gastritis. Within this period, the importance of the findings of gastritis, atrophy, and metaplasia in Correa's chart in 1992 was realized, and these findings were included in the first classification. However, due to differences between observers in the rating of especially chronic gastritis and atrophy over time, the Sydney classification was reviewed, and a visual analog scale was

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prepared by preserving the basic principles. Despite all these efforts, inconsistencies, especially in the rating of atrophy, drew attention. Thus, the team that made the first Sydney classification put forward a metaplastic/nonmetaplastic atrophy rating in 2002 (1-7).

The morphological changes that are observed in a gastritis chart can be summarized as follows:

1. Epithelial degeneration
2. Foveolar hyperplasia
3. Mucosal hyperemia and edema
4. Neutrophilic infiltration
5. Eosinophilic infiltration
6. Mononuclear inflammatory cell infiltration
7. Lymphoid follicles
8. Atrophy
9. Intestinal metaplasia
10. Endocrine cell hyperplasia
11. Parietal cell alterations

APPROACH TO GASTRIC BIOPSY

Acute

- Edema, congestion, hemorrhage
- Acute inflammation (neutrophil, eosinophil)
- Erosion, ulcer

Chronic

- Chronic inflammation (lymphocyte, plasma cell)
- Lymphoid aggregate, follicle
- Atrophy
- Metaplasia (intestinal, pyloric, pancreatic)

Specific (Lymphocytic, Eosinophilic, Granulomatous)

Reparative, Reactive

- Regenerative activity
- Foveolar hypertrophy
- Granulation tissue

SYSTEMATIC ANALYSIS OF BIOPSY

- Localization- corpus, fundus, or antrum
- Distribution of gastritis (pangastritis)
- Gastritis-gastropathy differentiation

CHANGES RELATED TO BIOPSY

- Edema
- Vascular dilatation
- Hemorrhage in focal lamina propria
- Flattening in surface epithelia (there is no epithelial degeneration or acute inflammation)

ACUTE GASTRITIS

Classification

Hemorrhagic, nonhemorrhagic, erosive, nonerosive, diffuse, and intense (Figure 1).

Etiology

- Medication, uremia, ischemia, shock, corrosive agent, radiation, sepsis, trauma, acute alcohol, severe burns, alkaline reflux, surgery

Physiology

- Decrease in mucus secretion
- Decrease in mucosal blood flow
- DNA, PG synthesis
- Decrease in mucosal barrier

Endoscopy

- Stress, fundus-corpus; NSAID, antrum
- Multiple round-shaped severe erosions with a diameter of several millimeters.
- Mucosal edema, hyperemic

ACUTE GASTRITIS (Acute erosive/hemorrhagic gastritis-tress-induced gastritis)

This is a transient type of gastritis that has an acute beginning, and it causes gastrointestinal pain and hemorrhage. It can develop in a hemorrhagic or nonhemorrhagic, ulcero-erosive or nonerosive manner, and it develops as a result of the stress that the mucosa is exposed to.

1. Physiological stress

Severe burns, trauma, SSS injury, etc.

2. Toxic stress, medication, especially NSAII

Corrosive substances, alcohol, bile reflux, etc.

3. Hemodynamic stress

Hypovolemia and shock, ischemia, hypotension

Morphological findings

Sharply circumscribed, superficial erosions that are generally smaller than 2 mm. These erosions are typically multiple, and they have a tendency to occur in proximal. Ulcerations are smaller than 1 cm, and the base is grayish green, sanguineous, and slightly swollen.

ACUTE GASTRITIS

Microscopy

- Hemorrhage and edema in superficial lamina propria
- Mucosal necrosis, neutrophil infiltration (low)
- Regenerative epithelium, syncytial glandular structure
- Erosive surface epithelium

Differential diagnosis

- HP Chronic active gastritis
  Lymphoplasmacytic inflammation
  Neutrophilic cryptitis
- Dysplasia
  Nuclear stratification

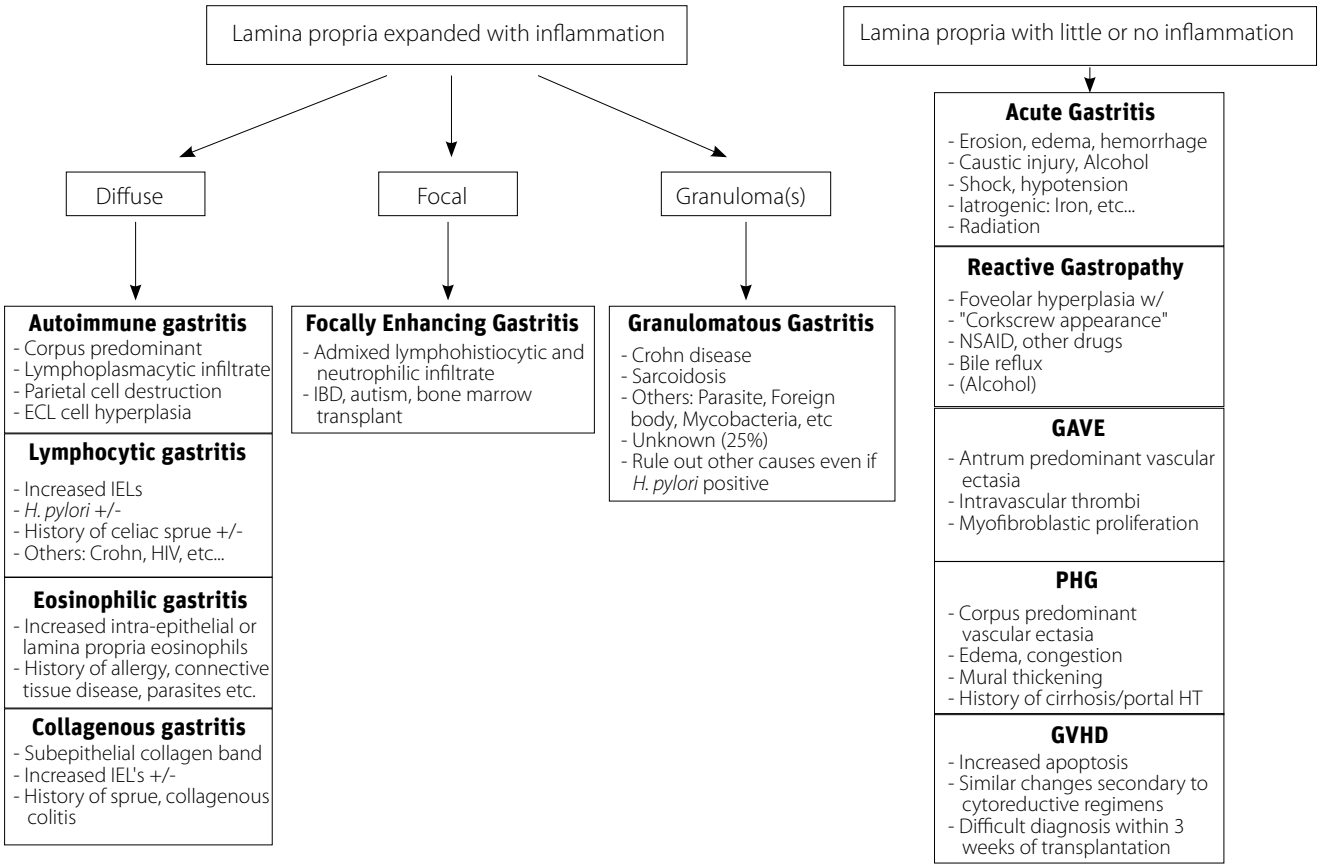

Figure 1. Schematic approach to the diagnosis of non-*Helicobacter pylori* gastritis

Hyperchromasia
Increased mitosis, regenerated epithelium amphophilic cytoplasm, regular nuclear contour

- Chemical gastropathy
  Mucosal elongation
  Smooth muscle hyperplasia
  Regenerated change
- Biopsy trauma: clinical history, endoscopic findings

NSAI usage

Mucosal erosion, petechial telangiectasia, acute hemorrhagic gastritis, erosion, loss in glands

ACUTE EROSIVE GASTRITIS

During acute phase

- Vascular congestion
- Edema and hemorrhage in lamina propria
- Superficial necrosis
- Polymorphic leukocyte in glands and pits
- Ulcer and erosions in surface epithelium
- Superficial fibril deposits

During the recovery phase

- Nuclear hypertrophy, epithelial regeneration
- Pit elongation
- Mucus depletion
- Mitosis

Mucosal changes

Variable
Slight congestion, edema
Superficial erosion
Massive necrosis
Deep ulcers
Inflammation degree depends on the severity of the injury

During recovery

Regenerative changes
Foveolar hyperplasia

"Acute hemorrhagic gastritis" related to NSAI and alcohol
Slight or no inflammation

CHRONIC GASTRITIS

- HP-related
- Autoimmune Gastritis
- Atrophic Autoimmune Pangastritis
- Metaplasia

Classification of gastritis - Etiologic classification

- HP-related gastritis
- Other gastritis

Chronic *H. pylori* Gastritis - Histopathology

- **Amount of *H. pylori* microorganism**
  - Scarce
  - Colonies
  - Abundant
- **Severity of the inflammation: Chronic inflammation cell amount**
  - Mild
  - Medium
  - Severe
- **Activity of the inflammation: Amount of neutrophils**
  - None
  - Mild
  - Medium
  - Severe
- **Intestinal metaplasia**
  - Presence of goblet cells
  - Goblet HC + Paneth cell complete metaplasia
  - Prevalent/Focal
- **Atrophy: Mucosal thickness and decrease in the number of glands**
  - Mild
  - Medium
  - Severe

CHRONIC GASTRITIS

There are three different forms of chronic gastritis:

- Antral
- Fundic
- Multifocal

HP-RELATED GASTRITIS

Clinical

80% asymptomatic
15%-20% morbidity
HP virulence?
Host immune response?
Accompanying factors: Smoking, nutrition, etc?
Dyspeptic complaints, nausea vomiting, anemia...

Endoscopy

Variable. Affects the antrum in the beginning and advances to the proximal in time. Corpus-oriented colonization in those who receive antacid treatment.

HP identification

Noninvasive clinical tests

Serum IgG antibodies (ELISA)
HP antigen in stool
Urea breath test (radioactive urea)

Invasive clinical tests

Rapid urease test (CLO test), culture, molecular tests (PCR)...

HP in tissue

Hematoxylin-eosin
Histochemistry
Immunohistochemistry
Electron microscopy

***H. PYLORI* - GENERAL DESCRIPTION**

***Helicobacter Pylori* (HP)**

H. pylori is a curved, gram-negative bacterium that has flagella. 3.5x0.5 µm.
1984- Warren-Marshall

Epidemiology

Fifty percent of the world's population is infected with *H. pylori*.

This rate is 70% in developing countries, and its prevalence in our country is 59%-82%

(TURHEP, GÖRHEN, DİSPEN).

Transmission: Human beings are the only known hosts. It can be transmitted via oral-oral, fecal-oral, and environmental factors.

PATHOGENESIS

Features that make it easier to survive in the stomach (virulence factors):

- Urease enzyme: It produces ammonia and carbon dioxide from endogenous urea, and it tampons the acid around it. It lives in a urease cloud.
- Motility (flagella): Enables it to swim in viscous mucus.
- Proteases: Melt the mucus.
- Adhesins: BabA and LewisB bind the blood-type antigens, and this enhances the bonding with cells that carry these types of antigens.
- Toxins: CagA ("cytotoxin association gene A")

More frequent in the HPs of societies with higher rates of stomach cancer. VacA ("vacuolating cytotoxin gene A"), which is responsible for cell bonds, polarity, and differentiation, is present in every HP strain. It forms vacuoles in the cell. It facilitates the nutrition of the bacteria. It inhibits apoptosis.

Strains with high virulence are cagA-, vacAs1-, iceA1-positive.

HP in the tissue

Histochemistry

Giemsa, toluidine blue, Alcian yellow, Genta, Thiamine colors, Diff-Quick (Figure 2).

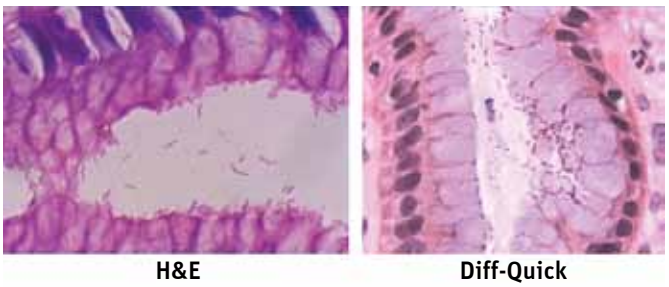

Figure 2. *H.pylori*'s bacillus with HE and Diff-Quick.

Silvering

Whartin Starry. The silver subsides and shows it to be bigger. Difficulty in implementation and artifacts. There are also automatized systems available.
Immunohistochemistry (IHK) is expensive for routine.
HP-negative chronic antral gastritis
Low HP density (dense IM, PPI, antibioterapy)
Coccoid form?

HP density

Should the densest surface or the average be assessed? Should the intestinal metaplasia (IM)surface be assessed?

It is harder for the bacteria to colonize the IM. Instead of average, the density of the gastric mucosa is more appropriate. The densest surface should be assessed.

Helicobacter pylori, the dominant factor in gastritis etiology, was actually identified by Kreniz and Luger for the first time on gastric secretions and on the necrotic material on the surface of ulcerated gastric carcinoma. In 1924, Luck and Steh identified evident urease activity in the stomach. In 1939, Doenges showed spirochetes in the stomachs of 43% of 242 autopsies. Then, in 1979, Fung identified a spirochete in the curves of surface mucus cells in chronic gastritis, and in 1983, Warren and Marshall showed that this bacteria had similar features with campylobacters, and the bacteria was named C. PYLORIDIS in 1985.

Then, plenty of bacteria, which showed similar growth to gram-negative bacteria, in a medium that was coincidentally planted and left unattended before Easter were found 5 days later. In 1994, bacteriologists included the bacteria in the Helicobacter group due to its features, such as denitrification, hippurate hydrolysis, and sensitivity to cephalotin.

Pathogenesis

Apical HC membrane, intercellular junction, weakens the bonds, downwards penetration, intercellular space and LP leukocytes, cytokines, growth factors... "Cellular-humoral response."

HP AND 2005 NOBEL MEDICINE PRIZE

Robin Warren (Pathologist)

Barry Marshall (Gastroenterologist)

Peptic ulcer - an infectious disease!.. Barry Marshall and Robin Warren, who with tenacity and a prepared mind, challenged prevailing dogmas… By using technologies generally available…

Helicobacter pylori can hold any part of the gastric mucosa, but it most frequently settles in the antrum and cardia, and it often advances to the fundus with treatment. HP infection starts as acute gastritis, causes neutrophilic infiltration in the cervix portion of the gastric pit, damages the epithelia with neutrophils and HP, and causes desquamation, and as a result, hyperplasia develops in order to replace dead cells.

The inflammation process is followed by erosion, ulceration, and loss in mucosal barrier. Neutrophilic infiltration in acute gastritis is rapidly followed by chronic inflammation. Lymphocytes, plasma cells, macrophages, eosinophil leukocytes, and cells get involved in the process. With the eradication of HP, neutrophils rapidly disappear while eosinophils disappear later. Atrophy and lymphoid follicles are more resistant, and if polymorphonuclear leukocytes are still observed despite treatment, HP should be examined again.

Atrophy of the gastric mucosa makes the mucosa thin and thereby causes severe mucosal injury.

As a result of the destruction of glands along with mucosa or of the glands that get damaged due to prolonged inflammations, atrophy is formed. After the atrophy develops, intestinal metaplasia replaces gastric mucosa.

Other changes observed in HP gastritis

Changes in surface epithelium

Damage, erosion, and loss of mucus.

The differences from artifact separation are fibrin, neutrophils. and regenerative changes.

Foveolar hyperplasia

Increase in length and curving of foveola.

Causes of foveolar hyperplasia:

- Chemical gastropathy
- hyperplastic polyp
- Menetrier's Disease
- Juvenile polyposis
- Ulcer and regeneration adjacent to stoma (3)

Regenerative changes

The proliferative compartment expands, and foveolar hyperplasia is observed. It is difficult to distinguish atypical regenerative findings from dysplastic lesions.

Pancreatic acinar metaplasia

Lobules that resemble pancreatic acinus

In autoimmune gastritis
In cardia
Along with other metaplasia
In intestinal metaplasia focus in antrum
Thin granulose and acidophilic in apical
Basophilic in basal. Cells with wide cytoplasm enclose the smooth muscle cells.

Pseudopyloric metaplasia
In corpus...
Difference from real "pyloric" gland
No G cells that produce "gastrin"
Contains enterochromaffin-like (ECL) cells
They excrete pepsinogen I as well as pepsinogen II.

When it is prevalent and if the localization of the biopsy in atrophy is not known, it is hard to diagnose.

IHK: Gastrin (-) (7)

Lymphoid follicles
There are no lymphoid follicles in normal stomach mucosa.

Its presence indicates the presence of HP.

However, it may not disappear months or years after eradication.

Attention! Wide and irregular follicles should be examined in terms of MALT lymphoma.

Endocrine cell hyperplasia
It is more apparent in atrophic gastritis. Hyperplasia may be "linear" or "micronodular." Dysplasia and endocrine may turn into tumor.

PPI-related changes
It is especially apparent in oxyntic mucosa. Vacuolar changes in gland epithelium, acidophil, protrusions like "clout nails" towards lumen, hyperplasia in smooth muscle fibers in antrum, vacuolization in parietal cells, and cystic changes in mucosa can be given as examples.

FREQUENTLY USED TERMINOLOGY IN HP GASTIRITIS

- The term **ACTIVE GASTRITIS** is used to express presence of chronic inflammation that accompanies enzymatically active neutrophils. Chronic inflammatory response is limited to superficial mucosa in the beginning (**superficial gastritis**), and then, it becomes deeper, and T-lymphocytes increase both in epithelium and in lamina propria.

- The evidence of lymphoid follicles that contain or do not contain germinal centers is identified as FOLLICULAR GASTRITIS. In fact, these lymphoid follicles show immune response to bacteria. If there are wide and irregular lymphoid follicles or lymphoid follicles that cover most of the mucosa, MALT lymphoma diagnosis should be considered.

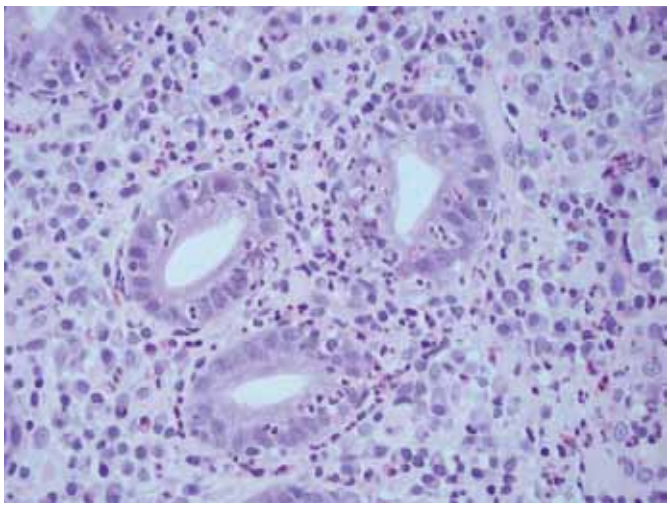

Figure 3. Glandular microabcess with PNL.

Superficial gastritis
Band-shaped in superficial mucosa
Lymphocyte, infiltration of plasma cells

Follicular gastritis

ACTIVITY: Polymorphonuclear leukocytes (PNLs)
Polymorphonuclear leukocytes activity is a good indicator of "active" or "acute" inflammation. It is a critical indicator for HP (it rapidly disappears in the days following the treatment).

Mild: Scarce neutrophils

Moderate: Apparent neutrophils in glandular epithelium and foveola

Severe: Mucosal erosions and glandular microabscess (Figure 3).

There is PNL in the biopsy but I cannot find HP Am I missing?

1. Cases where HP gastritis is present but cannot be located: Prevalent intestinal metaplasia, ulcer/erosion, PPI usage, antibiotic usage for another reason, Helicobacter heilmannii gastritis.

2. Gastritis that is not HP-related and that shows focal chronic active inflammation, carditis, reactive gastropathies, Crohn gastritis, or infectious (fungal, viral, etc.) gastritis.

INLAMMATION: Mononuclear inflammatory cells
What is normal is not known. In total, 2-5 lymphocytes, plasma cell, macrophage in "expected" limits in 1 BBA.

Table 1. Updated Sydney Classification

Feature	Definition	Gradind Guidelines
Chronic inflammation	Increased lymphocytes and plasma cells in the lamina propria	Mild, moderate, or severe increase in density
Activity	Neutrophilic infiltrates of the lamina propria, pits, or surface epithelium	Less than one third of pits and surface infiltrated = mild; one third to two thirds = moderate; more than two thirds = severe
Atrophy	Loss of specialized glands from either antrum or corpus	Mild, moderate, or severe loss
Intestinal metaplasia	Intestinal metaplasia of the epithelium	Less than one third of mucosa involved = mild; one third to two thirds = moderate; more than two thirds = severe.
Helicobacter pylori	*H. pylori* density	Scattered organisms covering less than one third of the surface = mild colonization; large clusters or a continuous layer over two thirds of surface = severe; intermediate numbers = moderate colonization

Plasma cells are normally absent or only a few in number; 3-5 plasma cells that come together between foveolae or glands means "mild" chronic inflammation.

Lymphocytes <5/100 epithelium cell.

Lymphocytic gastritis if this increases?

Lymphoid gathering cannot be found in a lamina propria that has not encountered HP.

Helicobacter pylori may exist for years after its eradication. The Sydney system suggests that chronic inflammation rating be done far from lymphoid follicles (8).

Chronic gastritis according to 1994 Sydney Classification

1. ACUTE
2. CHRONIC

NONATROPHIC - apparent gastritis in antrum - *H. pylori*, diffuse antral gastritis, pangastritis, superficial gastritis, type B

ATROPHIC - Corpus dominant - Autoimmune, type A
Multifocal atrophic - *H. pylori*

3. SPECIAL TYPES - and Gastropathy - Eosinophilic, lymphocytic, infectious, etc.

SYDNEY 2002 CLASSIFICATION

Due to the different points of view among gastrointestinal pathologists, especially about atrophy, atrophy and intestinal metaplasia were reviewed again. Two main phenotypes of chronic gastritis in the new description of atrophy were classified as:

- **Atrophic**
- **Nonatrophic**

Updated Sydney Classification (Table 1).

Points to take into account while making the Sydney classification:

1. Consisting of two from the antrum, two from the corpus, and one from the incisura angularis, five biopsies should be taken in ideal conditions from both the small and the big curvatures. The biopsy from the antrum should be taken 2-3 cm far from the pylorus, and the biopsy from the corpus should be taken 8 cm far from the cardia.

   The biopsies should be tagged and sent in three separate bottles (9).

2. The pathologist should be aware of the endoscopic findings, history of the patient, and the part of the stomach that the biopsy was taken from while evaluating the biopsy.

3. The biopsy sample that will be taken in the full layer from the mucosa should be determined in appropriate conditions; it should be placed vertically to the mucosa surface, and sufficient mass incision should be taken.

4. Appropriate histo/immunohistochemical stains should be used in order to make a reliable rating of HP.

5. *H. pylori*, chronic inflammation, PNL activity, atrophy, and metaplasia should be rated and located in each gastritis chart.

6. If there is an intense inflammatory reaction in the biopsy, atrophy rating should be avoided, and atrophy should be evaluated in the ambiguous group. However, the term atrophy should be used if there is intestinal metaplasia accompanying the inflammation. If there is atrophy both with and without metaplasia in the same biopsy, it is a better approach to evaluate the atrophy with metaplasia, since the metaplasia increases the risk of cancer.

7. If the metaplasia is limited to the foveolar epithelium and has not replaced the gastric glands completely, atrophy should not be referred. In this case, the lesion may be described with a metaplasia that is limited to the foveolar-focal or partial metaplasia.

8. While atrophy without metaplasia is being evaluated, the number of glands in x40 enlargement should be taken as

the morphological criteria. If the oxyntic tubules get shorter, the interglandular distance expands, and additionally, pseudopyloric metaplasia develops; a distinction from the normal antrum mucosa is not possible. In this case, a diagnosis of atrophy can be made only with the endoscopic findings.

Rating according to the updated Sydney classification

In stomach biopsy:

- Mononuclear inflammatory cell infiltration
- Activity, PNL infiltration
- Atrophy
- Intestinal metaplasia
- Rating of HP presence is, according to the visual analog scale, classified as mild, medium, and severe (10).

Chronic inflammation: In normal gastric mucosa, 2-5 lymphocytes, plasma cells, and macrophages can be accepted as normal; in fact, plasma cells are either nonexistent or very rare in healthy people. While evaluating chronic inflammation, it is necessary to evaluate places far from lymphoid follicles.

Activity: The severity of the intraepithelial PMNs is the most sensitive indicator of mucosal injury and presence of *H. pylori*, and they are the quickest cells to disappear with treatment.

Atrophy: Loss of glandular tissue is considered atrophy. Since atrophy is one of the most important steps of gastric carcinogenesis, the diagnosis and rating of atrophy are very important.

Intestinal metaplasia: Intestinal metaplasia in gastric mucosa is diagnosed with the presence of goblet cells, absorptive cells, and colonocytes that contain mucin. Since the lesion is often patch-like, it is important to identify the location of biopsy (11).

Complete: Goblet cells that contain acidic mucin and absorptive enterocytes with brush borders.

Incomplete: Irregularly shaped goblet cells and immature-intermediary mucus cells

Type II A or type II: the ones that contain acidic sialomucin

Type II B or type III: the ones that contain sulfomucin

Since pseudopyloric metaplasia often accompanies autoimmune gastritis and endocrine cell hyperplasia, it is important to diagnose. This kind of metaplasia should also be accepted as evidence of atrophy.

H. pylori: *H. pylori* activity in the stomach should be evaluated in places where there is no intestinal metaplasia.

HP GASTRITIS ACCORDING TO THEIR PHENOTYPIC AND TOPOGRAPHIC FEATURES

Non-atrophic gastritis

Sydney

Antral predominant gastritis

Non-atrophic pangastritis (or corpus dominant/predominant gastritis)

Atrophic gastritis

Sydney (Autoimmune gastritis/Multifocal atrophic gastritis)

Antrum dominant (limited to antrum/antral predominant) atrophic gastritis

Corpus dominant (limited to corpus/corpus predominant) atrophic gastritis

(Autoimmune gastritis is also a type of corpus-limited atrophic gastritis)

Another classification

- Non-atrophic antral predominant gastritis
- Non-atrophic corpus predominant gastritis
- Non-atrophic pangastritis
- Antrum-limited atrophic gastritis
- Multifocal atrophic gastritis

Importance

Antral predominant non-atrophic gastritis

The most common form of HP gastritis.

Acid secretion could be normal or increased.

The risk of duodenal ulcer is high. The risk of gastric cancer is low.

Corpus-predominant non-atrophic gastritis

It is generally seen in those who use PPI.

Pangastritis (or corpus dominant/predominant non-atrophic gastritis)

Acid production decreases. Gastric ulcer is common.

The risk of multifocal atrophic gastritis, metaplasia, and cancer is high.

Corpus dominant (limited to corpus/corpus predominant) atrophic gastritis

The risk of cancer has increased in these cases.

It is also called autoimmune gastritis.

TOPOGRAPHIC EVALUATION... WHEN CAN IT BE PERFORMED?

The Sydney system/OLGA system suggests that a full set biopsy be taken in order to make a topographic classification. Topographic interpretation can only be made if there is a full set, appropriate tagging, and endoscopic report.

How should we report if the biopsy is not full set?

In fact, most HP gastritis and non-HP gastritis/gastropathies could be evaluated with a few samples.

However (attention)
Systematic sampling and tagging is necessary for
Atrophy rating-staging

Metaplastic Atrophic Gastritis (MAG)-Autoimmune distinction
Pseudopyloric metaplasia evaluation (if there is no gastrin IHK)
Otherwise, interpretation regarding topographic dispersion should be avoided.

Even in benign lesion diagnosis, biopsies should be taken from the right place, with the sufficient amount. For instance, since the microorganisms may be dispersed in a patch manner in Helicobacter pylori gastritis, Helicobacter pylori may be negative if multiple samples are not taken from different localizations. Similarly, if the biopsy is taken from the middle and surface of an ulcerous lesion, a carcinoma that causes ulceration underneath or a lymphoma infiltration cannot be detected, since only an inflammatory exudate and necrosis will be seen.

The size of the biopsy is also important. In very small mucosa biopsies, even the diagnosis of benign lesions is difficult. The presence, activity, and atrophy of a gastritis or intestinal metaplasia cannot be evaluated in small biopsies that contain only foveolar epithelium and too little lamina propria. In small biopsies taken from malignant lesions, a few groups of malignant cells or a few tumoral glands or a few malignant cells, a large part of which is in necrotic fragments, can be observed. Besides the high probability of a carcinoma or a malignant tumoral process, it may be difficult to make a final diagnosis. Collaboration of clinicians is very significant in this kind of case.

Technically, another important problem is the mechanical artifact that is made by the biopsy forceps. When the benign nature glands get squeezed and lose their normal shape as a result of contusion artifacts, they may face carcinoma. Since the cell nuclei in the artifacts, which are at the margin of the biopsy, are stained larger and darker than normal, they may be thought to be dysplasia or carcinoma. The mononuclear cells that are in the normal limits in the mucosa may appear to be in great numbers as a result of contusion artifacts and thus be thought to be inflammation or lymphoma infiltration.

Another condition for a correct diagnosis is an examination in incisions that are prepared in optimal conditions that display full-layer mucosa and that are stained with well-oriented hematoxylin-eosin (H.E). In addition to the fact that histochemical, immunohistochemical, and molecular methods are frequently used and are helpful in differential diagnosis, the golden standard is still the examination of incisions that are stained with H.E.

Despite some other problems that are faced in the evaluation of benign lesions in endoscopic biopsies, the main problem is the differential diagnosis of whether the lesion is neoplastic or non-neoplastic and how the follow-up and the treatment of the patient will be directed afterwards.

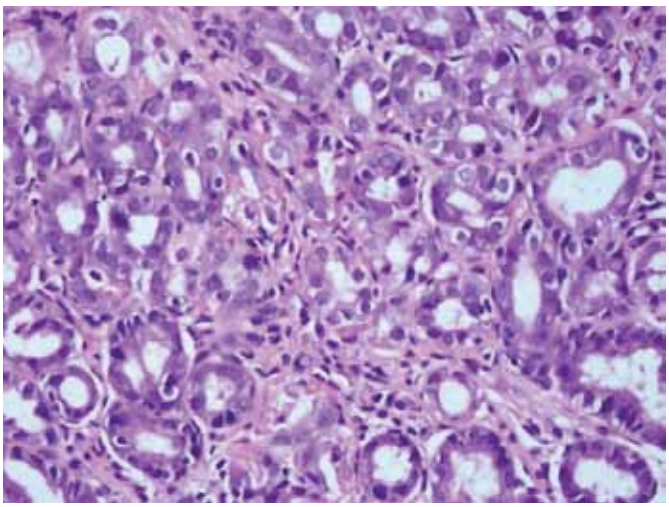

Figure 4. Nuclear hiperkromazi, nucleus/stoplazma percent increase seen in the regenerative atypia.

Diseases that are related to *H. pylori*

- Chronic gastritis - 90%
- Peptic ulcer - 95%-100%
- Gastric adenocarcinoma - 70%
- Gastric lymphoma (MALT lymphoma)
- Reflux esophagitis?
- Non-ulcer dyspepsia

HP AND GASTRIC CANCER

Helicobacter pylori prevalence is 80%. Why do some people have cancer while others do not?

Why is there an apparent atrophic background in some cancers while there is none in others?

Inflammation pattern- risk of cancer... IL-1 beta gene polymorphism?

Every step of the cascade... More apparent in societies where the risk of gastric cancer is high!

HP is a strong risk factor in distal gastric cancers. But, its relationship with gastric cardia? (lowers the risk?)

No genetic-molecular difference in HP-related/non-HP tumors!

WHO-IARC... HP type 1 carcinogen!

Chronic inflammation- increased cellular "turn-over"- increased mitotic failure - increased rate of mutation (12).

Correa pathway / Correa cascade
Chronic gastritis
Atrophic gastritis

Intestinal metaplasia
Dysplasia and

Gastric cancer

In lesions that are formed by Helicobacter pylori or non-steroidal anti-inflammatory drugs (gastritis, ulcer/adjacent to erosion) and especially in the intestinal metaplasia zone, it could be difficult to differentiate regenerative changes from low-grade dysplasia.

Besides the fact that ulcer/erosion adjacency or intense active inflammation is mostly considered to be in favor of regeneration, it should not be forgotten that active inflammation can also be observed in low-grade dysplasia. The regenerative changes being limited to the glands' proliferative zone and not advancing to the surface epithelium and absence of structural deformation are useful for diagnosis.
In the Padua classification that was made in 2000, dysplasia was named non-invasive neoplasia (NIN) and "indefinite" group lesions, in which regenerative atypia and dysplasia (NIN) could not be differentiated, and was classified into two subgroups in order to make a better identification.

1. Foveolar hyperproliferation (seen with erosion or ulcer, no intestinal metaplasia)

2. Hyperproliferative intestinal metaplasia (back-to-back gland pattern, consists of medium/high number of intestinal glands with mitotic character). The main problem in the diagnosis is the hyperproliferative intestinal metaplasia type.

Atypia is the most important histopathologic finding that determines the lesion's nature. In general, it shows that the cell's proliferative activities, such as hyperbasophilia, nuclear and nucleolar growth, increased mitotic activity, and decreased cell maturation, have increased. In addition to the fact that it can be seen in benign lesions, it is a feature of real neoplastic epithelium, such as dysplasia or cancer.

Atypia is in 3 main types:

1. Reactive atypia: It develops as a response to tissue injuries, such as acute inflammation or radiation.

2. Regenerative atypia: It develops as a regenerative response to benign ulcer or erosion (Figure 4).

3. Precancerous atypia (dysplasia/intraepithelial neoplasia): It develops as a neoplastic process without relation to reactive or regenerative causes, and it is a change of epithelium that has a risk of developing cancer.

In addition to the aforementioned cytologic features of atypia, there are also structural deformations, such as nuclear polarity loss in epithelium in real dysplasia, multiple ranks, as well as presence of abnormal mitosis, back-to-back gland pattern, budding, and papillary formation (13).

In endoscopic biopsies, after diagnosing dysplasia, the second crucial point is the distinction of high-and low-grade dysplasia, and especially in an intramucosal carcinoma diagnosis, various histopathological approaches among pathologists is a much-debated issue. Especially, this difference is presented by Japanese and Western pathologists in great numbers of studies (14). Although an apparent invasion is not seen in most of the high-grade dysplastic lesions, Japanese pathologists evaluate it as intramucosal carcinoma (15). While Japanese pathologists evaluate only in accordance with the degree of cytologic and structural atypia, the incidence of lamina propria invasion is an indispensable criterion in the West (16-18). In order to prevent this difference and to make the whole world use the same terminology, the Padua and then Wien classifications were made, and based on the Wien classification, the WHO-2000 classification was made in 2000 (19,20). There has not been any change in the WHO-2010 classification.

Diagnosis according to Western pathologists:
- High-Grade Dysplasia

Diagnosis according to Japanese pathologists:
- Intramucosal Carcinoma

In the grading of dysplasia, the triplet system (low-, medium-, high-grade dysplasia) had been used for many years. However, the dysplasia classification formed by Riddell et al. in 1983 in inflammatory bowel diseases was found to be very practical and was applied to the stomach as well. It started to be used in many centers in the form of a doublet grading system, which was dysplasia-negative, indefinite group for dysplasia and low or high grade for dysplasia positive. Cases diagnosed as "indefinite dysplasia" in which dysplasia and regenerative/reactive atypical changes can not be differentiated are immediately recommended to have a certain diagnosis by a new biopsy or biopsies of pursuance after the treatment. The answer to the question about whether it is real dysplasia or regenerative/reactive hyperplasia is one of the most important problems of this routine. The increase of the expression and its discontinuity in the surface ımmunohistochemical that shows the activity of proliferative Ki67, PCNA, the existence of the expression of P53, intestinal differentiation (cdx2), immortalization (hTERT), MUC5AC, MUC 6 expression ptosis, recently defined α-Methylayl-CoA-Racemase (AMACR) expression are used as assistant methods in dysplasia diagnosis (21). However, in most of the studies, it is seen that molecular markers are limited in distinguishing the atypical hyperplastic lesions from low-grade dysplasia (NİN). The second important point in endoscopic biopsies after the diagnosis of dysplasia is made is correct grading, because the biological meanings and treatment approaches of low- and high-grade dysplasia are very different to each other. As can be seen, there are still no objective measures put for-

ward in dysplasia diagnosis and grading. The support of immunohistochemical and other molecular methods is limited. Incisions stained with gold standard H.E. and another pathologist's (experienced in gastrointestinal systems) confirmation of the diagnosis are recommended.

ATROPHY

In its new description, atrophy is described as "loss of the appropriate glands (native glands in a specific surface);" so, metaplasia is added to the description of atrophy.

Two kinds of atrophic lesions are defined:

1. With the replacement of native glands by epithelia-showing metaplasia-atrophy related to metaplasia

2. The decrease of the density of native glands and characterized by the increase in interglandular extracellular matrix-nonmetaplastic atrophy

It is possible to observe both metaplastic and nonmetaplastic atrophy in one patient; in such cases, as metaplasia increases the risk of cancer, priority should be given to the diagnosis of atrophy related to metaplasia.

"the loss of the glandular tissue and thinning of mucosa," in the original Sydney system.

- Functional atrophy (Atrophy Club).
- It is normal to have 4-5 lines of glands on the muscularis mucosa
- Antrum, corpus
- It is difficult to determine the grade of atrophy in the antrum rather than corpus. Normally, in the antrum, glands are in loose stroma and gastric pits are longer, and there is dense inflammatory cell infiltration in HP. Glands are denser in the corpus.
- Parietal cells and core cells lie on the neck of the gland. The reticulin dips among the pits. "the loss of appropriate glands"(22).

Negative for atrophy: There is no indication of the loss of the gland when a sufficient number of samples is taken. If limited intestinal metaplasia in the minimal focus or in foveola does not cause loss of gland, it should be evaluated as negative for atrophy.

Indefinite for atrophy: If there is apparent inflammation, lymphoid aggregates, and follicles in the lamina propria, antral glands and oxyntic glands secreting mucin could be masked by inflammation. While defining the phenomenon, it is necessary to use the description of indefinite for atrophy and to ask for a new biopsy again in such a case. Generally, atrophy indications retreat after several months of successful eradication treatment. However, if the inflammation is with all of the intestinal metaplasia of the glandular area, it should be evaluated as atrophy.

CHRONIC GASTRITIS STAGING (OLGA staging)

Operative Link for Gastritis Assessment (OLGA)
Gastroenterologists and pathologists
It is a system "staging" morphologic changes (atrophy) according to increased risk of cancer from 0 to IV.

Atrophy: None/metaplastic/nonmetaplastic atrophy/indefinite atrophy

ATROPHY

Mild: 1%-30%
Medium: 31%-60%
Severe: 61%-70% (the cystic dilatation of the gland is together with the epithelial atypia and intestinal metaplasia); 16 times increased risk of malignancy.
The risk of malignancy increases by 11% when atrophy and intestinal metaplasia are together.

HP GASTRITIS EVALUATION

Helicobacter pylori gastritis is a perpetual and "chronic" gastritis.

Some of the changes are not characteristics of HP gastritis.

Grading	**Staging**
Sydney Classification (1996-Houston)	OLGA Staging system (<10 years)
Intensity of observed changes	Gastritis- atrophy-cancer relation
Follow-up?	Whom to follow?
	It grades atrophy

Important points to pay attention to in atrophy associated with metaplasia

- If the metaplastic change is limited in the foveolar part of the gastric gland, atrophy should not be mentioned. The term atrophy should be used when all segments of the original glandular unit go to metaplasia.
- Goblet cells, scattered and few in number, are a frequent indication, especially in *H. pylori*-related gastritis. These lesions should be depicted as limited in foveola, partial, etc.
- Metaplastic atrophy should be classified as mild, medium, and severe. There is sporadic intestinal metaplasia of a gland in atrophy with mild metaplasia, and there is prevalent metaplasia in the severe form.

METAPLASIA

- Pyloric
- Intestinal
- Pancreatic
- Cilia cell

Intestinal and pyloric metaplasia is frequent in HP.

Native glands can change positions with mucus cervix cells or mucus-secreting glands in oxyntic compartment- pseudopyloric metaplasia. This view is frequently associated with advanced autoimmune gastritis and endocrine cell hyperplasia. It should be evaluated as atrophy related with metaplasia in such cases.

It could be difficult to distinguish native glands replacing the nonatrophic antral gastritis and metaplasia with pseudopyloric oxyntic mucosa in the incisura angularis; in these areas, only intestinal metaplasia should be used to define gastric atrophy.

INTESTINAL METAPLASIA
According to histological features similar to colon and intestine
Brush border, paneth cell, goblet cell…
Mucin ingredient is evaluated as complete/incomplete
To determine the mucin ingredient
PAS
Alcian blue pH 2.5
Alcian blue pH 0.5
The combinations of these with high iron diamine are used.
It is related with HP.
As the required features are in the epithelium for adhesion, HP can not colonize in intestinal metaplasia areas.

Foveolar epithelium of gastric containing neutral mucin, pH 2.5, is stained pink with PAS-Alcian blue; acidic glycoproteins in intestinal metaplasia are stained with blue-purple.

As type III metaplasia has a more apparent relation with cancer, sulfomucin HID/AB with its special dye is stained brown, while sialomucin is stained blue. However, the requirement of the coloring should be debated, as it is difficult to distinguish metaplasia involving sulfomucin, and it requires expensive methods.

HELICOBACTER HEILMANNII (HH) GASTRITIS
Helicobacter Heilmannii, gram-negative bacillus
It is 5-9 µm longer than HP, and it has a spiral shape
It generally causes a milder focal gastritis in the form of a patch
More frequent in children
Infection: From livestock or pets

Alkaline Reflux Gastritis
Foveolar hyperplasia
Similar to hyperplastic polyp
Villiform transformation
Irregular glands containing gall crystals

Acute Suppurative (Phlegmonous) gastritis…
Generally old, alcoholic, addicted people
An acute chart that could be fatal
Agent factors are bacteria, such as streptococcus, staphylococcus, E. coli and proteus. (infectious gastritis)
It is frequently seen in laparotomy biopsies or autopsies
Dense submucosal and mural intense PNL infiltration, mucosal fall, and necrosis are seen frequently

CHRONIC REACTIVE (CHEMICAL) GASTROPATHY
It is more frequent in antrum
NSAI drug use
Gall reflux (stomach surgery)
Mucosal edema, congestion
Foveoler hyperplasia like "corkscrew"
Fibromuscular hyperplasia in LP
(increase of smooth muscle tendons, their stretching towards the surface)
Regenerative changes
Chronic inflammation is not as dense as HP
Erosion might develop
Infiltration of eosinophils

Differential diagnosis…
Regenerative mucosa shifts around the ulcer (presence of ulcer)
Foveolar hyperplasia related to HP
(presence of medium-severe inflammation on the ground)
Hyperplastic polyp (presence of endoscopic polyp)
Gastric Antral Vascular Ectasia (GAVE)

LYMPHOCYTIC GASTRITIS
Chronic gastritis continuing with the increase of intraepithelial T lymphocytes (İELs)

Etiology… most frequently, it accompanies gluten-sensitive enteropathy (40%) and HP gastritis (20%)

Histomorphological indications…

İEL >25 lymphocytes/100 epithelial cells
Both in the surface and in the foveolar epithelium
In HP gastritis, it is 1/10
Most of it is CD3 (+) T lymphocytes
CD8 coexpressed
Involvement is in the form of either patch or diffuse
Involvement of corpus is more frequent

Differential diagnosis… HP gastritis. Lymphoma
Treatment… Towards the accompanying pathology
Responds to steroids as well. It may regress spontaneously.

GRANULOMATOUS GASTRITIS
It is a **descriptive** diagnosis.
Infections
Tuberculosis, histoplasma, Taenia,
strongyloides, *H. pylori*
Systemic diseases
Crohn disease, Sarcoidosis, CVID,
Wegener granulomatous…
Foreign bodies: Suture material,
barium, mucus, "food granuloma"
Idiopathic; in 25% of the cases, there is no etiologic agent (it is also called isolated idiopathic granulmatous gastritis)
Clinic…It depends on the related illness.

Histology
Caseification necrosis - tuberculosis
Large compact granulomas surrounded by lymphocytes in normal mucosa - sarcoidosis
Eosinophilic infiltration - parasitic disease
Ulcer edge - "food granuloma"
Not having plasma cells - CVID
Localized in antrum, HP-negative focal chronic active gastritis - Crohn H.

GASTRIC CROHN DISEASE
The "gastric-dominant/gastric beginning" forms of the illness are <4% of all Crohn cases

Endoscopic changes or inflammation in 15% of people who have Crohn disease; microscopic mucosal changes or inflammation in 75%

The indications are the same with intestinal Crohn disease.

SPECIFIC GASTRITIS TYPES
Collagenous gastritis: It is characterized with the existence of subepithelial thick acellular collagen bands.

Radiation gastritis: It is scarcely seen; necrosis, edema, and mononuclear inflammatory cell infiltration are seen in fundic glands. It is a reversible event.

Infectious gastritis: It is a gastritis emerging from factors, such as mycobacterium avium intracellular, treponema pallidum. CMV observed in people who have immune deficiency.

Carditis: The inflammation of the cardia is generally with gastrointestinal reflux; if there is no *H. pylori*, generally acute inflammation is not seen.

COLLAGENOUS GASTRITIS
Etiology…
Unknown
Co-occurrence with other collagenous intestinal and autoimmune diseases
Both in pediatric and adult groups
Intestinal and autoimmune defects do not accompany in children.
Histopathology…
Subepithelial collagen thickening (> 10 µm) (on average 30-40 µm).
Surface epithelial damage and accompanying inflames
Involvement could be in patch form or diffuse (23)
Chronic or active inflammation, intraepithelial lymphocytosis, intestinal metaplasia±HP.

INFECTIOUS GASTRITIS
CMV gastritis...
It is seen in immunosuppressive people.
It is appropriate to take biopsy in ulcer lesions from the basis of the ulcer.

Fungis
Candida...
Colonized in 20% of benign gastric ulcers …
Most of them recover with antacid treatment without the necessity of additional antifungal treatment.

Aspergillus (Mucor)...
The invasive forms are almost always fatal. It is an "emergency/panic" diagnosis.

PORTAL HYPERTENSIVE GASTROPATHY
Related to portal hypertension in cirrhotic or noncirrhotic patients.

Endoscopy: appearance like "snake skin" caused by mucosal edema and erythema

Antrum is typically preserved.

Histopathologic indications …
Dilate capils and vens in mucosa and submucosa.

Differential diagnosis ...
GAVE (fibrin thrombus) fibrovascular proliferation is seen.

AUTOIMMUNE GASTRITIS

Histomorphologic indications...
Changes are in oxyntic mucosa. Antrum is preserved.
1. Chronic gastritis (lymphoplasmocytic infiltration that is denser in depths of mucosa).
2. Atrophy (it is lost in oxyntic mucosa; parietal and chief cells)
3. Metaplasia (intestinal metaplasia, pseudopyloric metaplasia, pancreatic acinar metaplasia)
4. Neuroendocrine cell hyperplasia (linear or nodular)

Indications change according to the stage of the illness.
In Early Stage: dense inflammation, metaplasia in form of patch

In Fluoride Stage: diffuse inflammation, apparent atrophy, metaplasia, ECL-like neuroendocrine cell hyperplasia

In Advanced Stage: slight inflammation, apparent atrophy and metaplasia±foveoler hyperplasia, microcystic changes.

Mucosa may look like small intestine (complete intestinal metaplasia).

Autoimmune Gastritis
Synonym: Type A gastritis, fundic gastritis, diffuse corporal atrophic gastritis, autoimmune chronic gastritis

Epidemiology: Northern Europe - Scandinavia, in females

Etiology: Immune attack: In acid-secreting mucosa, a progressive destruction affecting mainly parietal cells and chief cells.
H. pylori: <20%

Laboratory: Anti-parietal HC, antibodies (+)
Anti-İF antibodies (+)

B12: Low (pernicious anemia)

Gastrin: Very high

Histology: KG, atrophy in oxyntic mucosa, metaplasia, NEH, G-HC hyperplasia in antrum.

Multifocal atrophic gastritis
Synonym: Peripheral chronic atrophic gastritis, peripheral metaplastic atrophic gastritis, atrophic gastritis type AB, atrophic pangastritis

Epidemiology: the whole world, female = male

Etiology: HP (mis-hygiene?) (frequent in Japan, rare in Africa)
HP: 90%-100%

Laboratory: Anti-parietal HC, antibodies: negative
Anti-İF antibodies: normal
B12: normal
Gastrin: normal or low

Histology: There is no NEH in the corpus.

AUTOIMMUNE GASTRITIS

It constitutes 10% of chronic gastritis. Hypochloride, achlorhydria progress with high serum gastrin. Generally, there is no symptom; 90% antiparietal cell immune bodies and 60% anti-intrinsic immune bodies are positive. Glandular atrophy, especially corpus and fundus mucosa, is dominant. Diffuse and deep lymphoplasmocytic infiltration is seen in the lamina propria. There is linear and nodular neuroendocrine cell metaplasia and parietal cell pseudohypertrophy. Oxyntic glands disappear and give their place to glands (pseudopyloric metaplasia) producing neutral mucin (periodic acid-Schiff-positive).

EOSINOPHILIC GASTRITIS

Diagnosis

1. Dense eosinophilic infiltration in stomach
2. Presence of GI symptoms
3. Excluding the pathologies that may cause eosinophils

Minimal eosinophil density?
At least 20 eosinophils/BBA
Involvement may be in the form of patch, or it may be prevalent.

Etiopathogenesis...
Genetic factors, food allergens, interleukins (especially IL-5, IL-3, and GM-CSF) and chemokines (CCL-5/RANTES, CCL-11/eotaxin)

Clinical...
Atrophy history, peripheral eosinophils, increasing of serum IgE 20% in pediatric age group
Nausea, vomiting, diarrhea, obstructive symptoms

Histomorphologic indications...
Mucosa is normal, erythematous, ulcerous, or hypertrophic.

Eosinophilic microabscess might be seen.

Differential diagnosis...
Parasitic infections, drug reactions, inflammatory bowel disease

Treatment and prognosis...
It gives a dramatic response to steroid.

GENERAL APPROACH TO GASTRITIS-SUMMARY

Most of the gastritis types can be recognized by H & E-stained tests. While evaluating biopsy, the answers to the questions below will ease the specific diagnosis towards the etiology.

1. Are there any indications of chronic gastritis? (lymphocyte and plasma cell infiltration in LP are chronic gastritis indicators, Sydney Classification)
2. Is there PNL in the mucosa? (it is an indicator of active gastritis)
3. Is there HP? (when needed, special stains could be used)
4. Is there glandular atrophy or intestinal metaplasia?
5. Is there any specific feature in the division of lesions (topography)? Is it antral predominant? Is corpus-fundus predominant? Is it holding the whole stomach?
6. Are there any special indications? (granuloma, foveolar hyperplasia, viral inclusion?)
7. Is an additional examination needed? What are the consequences?

CONCLUSION

Stomach endoscopic biopsies are made to determine the diagnosis of the illness, its stage, and follow-up after the treatment. It is very significant to collaborate with the clinician while evaluating endoscopic biopsies. Besides the clinical and laboratory information of the patient, the endoscopic appearance of the lesion should be known. The clinician and pathologist should use the same language and the same terminology. Although new classifications have been made to prevent the confusion of terminology in neoplastic processes recently, most of the centers around the world report non-invasive neoplasies without giving any certain diagnosis, by just commenting on it. Clinicians should understand what the pathologist wants to say, and pathologists should know the approach of the clinician (repetition of the biopsy, endoscopic resection, surgery).

There is HP in most of the stomach pathologies as the etiologic agent. No matter the factor is HP or other etiologic agent, the tissue gives similar responses. This is why clinical-endoscopic indications should be taken into consideration as well as histological indications, and the reports of the endoscopy should be seen. A good clinicopathologic correlation increases the accuracy of the diagnosis.

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