The Morphology of Gastritis

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Gastritis is a histopathologic diagnosis, which correlates poorly with both clinical symptoms of non-ulcer dyspepsia and endoscopic abnormalities. Worldwide, most cases of gastritis are due to \textit{Helicobacter pylori} and are characterized by a diffuse superficial antral gastritis. Chronic inflammatory cells and lymphoid follicles are present in the lamina propria. Neutrophils are present in the surface and pit-lining epithelium. In North America and Western Europe, reactive gastropathy due to duodenal reflux or non-steroidal anti-inflammatory agents is also common. In this condition, there is no increase in inflammatory cells, but the pit-lining cells become hyperplastic, and the pits have a corkscrew appearance. Most examples of multifocal atrophic gastritis are the result of long standing \textit{Helicobacter} gastritis, although there may be other causes as well. It is characterized by loss of glands in both pyloric and corpus mucosae with intestinal metaplasia of the surface epithelium. A subtype of intestinal metaplasia, in which sulphomucin (large bowel mucin) is present, has been associated with the development of distal gastric cancer. However, this association is relatively weak and is not considered useful for screening purposes. Gastric dysplasia may develop in areas of the stomach affected by intestinal metaplasia. High-grade dysplasia is a significant finding, with up to 60 percent of cases having coincident carcinoma and a further 25 percent of cases likely to develop an invasive malignancy within fifteen months.

CLASSIFICATION OF GASTRITIS

An etio-pathologic classification of gastritis is given in Table 1. This is derived from standard textbooks of pathology (1) and some original clinical (2) and morphologic (3) observations made several years ago. Classifications of this type, however, suffer because they mix entities that are based on a known single etiology with conditions that can only be described morphologically and may have several causes. These systems are illogical, but practical in the sense that they may be used as a basis for treatment decisions. With time, this classification will evolve as more information is gained into the different causes of gastritis.

The recently proposed Sydney system for the classification of gastritis (4) was intended to replace these mixed and incomplete classifications with one that was both logical and comprehensive. However, it also has faults in that it is not a true classification but is mainly a device for systematically recording in a logical fashion information of a descriptive nature. The Sydney system requires that two biopsies be taken from both pyloric and fundic mucosa and graded at both sites according to the severity of atrophy, inflammation, activity, intestinal metaplasia and the presence of \textit{H. pylori} organisms. Using the Sydney system as it was originally devised may lead to the generation of long complicated reports suitable for research protocols, but it is confusing to non-experts. It

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\textsuperscript{b}Abbreviations: MAG, multifocal atrophic gastritis; IM, intestinal metaplasia.
Table 1. Classification of gastritis.

| Acute gastritis:                                      |
|-----------------------------------------------------|
| Acute erosive gastritis                             |
| Suppurative gastritis                               |

| Chronic gastritis:                                    |
|------------------------------------------------------|
| Helicobacter gastritis                               |
| Multifocal atrophic gastritis                        |
| Autoimmune gastritis                                 |
| Granulomatous gastritis                              |
| Eosinophilic gastritis                               |
| Lymphocytic gastritis                                |
| Radiation/Chemotherapy gastritis                     |
| Viral gastritis                                      |
| Graft vs. host disease                               |
| Reactive gastropathy                                 |

was devised by a committee composed mainly of European pathologists and gastroenterologists, but, at the present time, it is not widely used in North America.

**REACTIVE GASTROPATHY**

Throughout the world, gastritis related to *H. pylori* infection is by far the most common cause of inflammation of the stomach, although in North America and Western Europe a reactive gastropathy secondary to drug therapy, especially non-steroidal anti-inflammatory agents (5), or duodenal reflux (6) is also frequent. Reactive gastropathy is thought to be the result of increased exfoliation of cells from the mucosal surface leading to increased proliferation of pit-lining cells. This is likely a secondary cytotoxic effect of drugs or a component of bile, such as lysolethicin. Morphologically, the gastric pits become elongated and develop a corkscrew appearance (Figure 1). The lining cells show cytoplasmic mucus depletion and have enlarged nuclei containing prominent nucleoli. Inflammation of the epithelium and the lamina propria is not present, although there may be capillary dilation giving rise to a profound congestion that can be endoscopically striking. This absence of inflammation is probably not surprising, since the pharmacologic action of non-steroidal anti-inflammatory agents is to suppress the inflammatory reaction. Reactive gastropathy is a chronic condition, which should be distinguished from acute hemorrhagic gastritis. Hemorrhagic gastritis may also be the result of ingestion of non-steroidal anti-inflammatory agents, particularly aspirin, and is characterized by the presence of fresh bleeding into the lamina propria with acute ulcers, usually superficial erosions. If ulceration occurs in reactive gastropathy, it is usually in the form of chronic ulcers that mimic peptic ulcers.

**AUTOIMMUNE GASTRITIS**

Autoimmune gastritis (the gastritis of pernicious anemia) occurs most commonly in individuals from Northern Europe, particularly Scandinavia (7). Typically, the corpus and fundus are most severely affected and develop an extreme degree of atrophy, so that the glands containing chief and parietal cells are almost totally destroyed (Figure 2). The surface and pit-lining epithelium undergoes metaplasia to an intestinal pattern. In advanced disease, there can be formation of Paneth cells and even rudimentary villi. The early stages (i.e., pre-atrophic) of autoimmune gastritis show a dense lymphoplasmacytic infiltrate surrounding the oxyntic glands with sparing of the superficial mucosa (8). It is presumed that the disease progresses by cytotoxic lymphocytes progressively destroying the specialized...
Figure 1. Reactive gastropathy, showing extreme tortuosity of the pits. Inset shows regenerative epithelium.

Figure 2. Autoimmune gastritis showing extensive intestinal metaplasia with complete loss of acid and enzyme secreting glands.
gastric body and fundic glands. Ultimately, the inflammation “burns itself out,” leaving a severely atrophic, but uninflamed mucosa. Typically, in autoimmune gastritis, the pyloric (antral) glands, which are exclusively mucus secreting, are preserved.

**HELIcobacter pylori Gastritis**

The histologic features of the early stages of *H. pylori* gastritis are well described (9, 10). The superficial lamina propria is expanded and contains an infiltrate of mature lymphocytes and plasma cells. Lymphoid follicles with germinal centers are present, although these may not be sampled in every biopsy. In active disease, the pit-lining and surface epithelium is infiltrated by neutrophils, and collections of neutrophils (pit abscesses) may be present within the lumen of the pits (Figure 3). In general terms, the intensity of the neutrophilic infiltrate parallels the numbers of organisms present (11). However, active gastritis is more severe in the antrum than it is in the fundus, although organisms may be seen at both sites. The pit-lining cells show a loss of mucus, often with a scalloping of the superficial cytoplasm, particularly in heavy infections. The nuclei are enlarged and vesicular with prominent nucleoli. At this stage of the disease, organisms are readily identified within the surface layer of mucus. They are particularly obvious at the site of intercellular junctions of the surface epithelium. A special stain is rarely needed to identify the bacteria, although a number are available (12, 13). They are best used when the initial routine hematoxylin and eosin stains are negative or for a follow-up biopsy following antibiotic therapy, when it is necessary to detect possible small numbers of residual organisms. Care should be taken to include as positive only the characteristic slender gull wing shaped bacilli. A number of fusiform bacilli or coci may occasionally be encountered, probably representing contamination from the oropharynx. Other types of *Helicobacter* that may rarely be encountered in gastric biopsies include *Helicobacter heilmanni* (*Gastrospirilum hominis*). This can be recognized on special stains as a tightly coiled spiral organism. After successful treatment with antibiotics, the bacteria and the neutrophilic infiltrate disappear within a matter of weeks (14). The chronic inflammation persists, at least initially.

In North America, it is unusual to find *H. pylori* gastritis in children, although in developing countries it can be present in 50 percent of individuals (15). In North American adults beyond the age of 60 years, serologic evidence of *H. pylori* infection is present in 40 to 60 percent of the general population (16). In developing countries, adult infection may be as high as 70 to 90 percent (15).

**Multifocal Atrophic Gastritis**

Multifocal atrophic gastritis (MAG) is a controversial diagnosis (17), which is not recognized by all authorities as a separate nosologic entity. Morphologically, MAG is characterized as a patchy disease involving both the antrum and the fundus. The changes are maximal along the lesser curvature in the region of the incisura (18). Histologically, there is extension of a chronic inflammatory infiltrate to involve the full thickness of the mucosa with an accompanying gland atrophy. Intestinal metaplasia is exceedingly common, if not universal (Figure 4). As the glands of the fundic mucosa atrophy, there is a reduction in acid output (19). Active inflammation, in the form of neutrophil infiltration of the surface and pit-lining epithelium, may or may not occur, depending on whether *H. pylori* organisms are present.

At the present time, it seems likely that most cases of MAG, at least those occurring in North America and Western Europe, are the result of ongoing *H. pylori* infection (20). The time scale for the conversion of an active superficial gastritis to an atrophic gastritis is unclear, but is probably several years. Many factors may influence this conversion, including host immunologic response, diet and strains of organisms of different virulence
Figure 3. *Helicobacter pylori* gastritis, showing the presence of reactive lymphoid follicles. Inset (left): neutrophilic infiltrate of pit epithelium. Inset (right): organisms on mucosal surface.

Figure 4. Multifocal atrophic gastritis showing mucosal inflammatory infiltrate with gland atrophy. Focal intestinal metaplasia is seen (inset).
(18, 21). The age at which infection is first acquired may also be important. In third-world countries, MAG is relatively common and is positively associated with the risk of developing gastric cancer (22).

**INTESTINAL METAPLASIA**

Intestinal metaplasia (IM) occurs almost universally in MAG, but may complicate other chronic inflammatory conditions also. These include autoimmune gastritis, gastric Crohn's disease and radiation gastritis. It has been divided into three types (23, 24). Each of these involve a change of the normal gastric surface epithelium to intestinal epithelium. In type I IM (Figure 5a), the stomach comes to resemble the normal small bowel with the presence of goblet cells and absorptive cells. In advanced cases, there may even be formation of rudimentary villi, and Paneth cells may be present at the base of the crypts. The mucin within the goblet cells is sialomucin, which stains positive with both periodic acid-Schiff and alcian blue at pH 2.5.

Type II IM is an incomplete form of type I. The normal neutral mucus of the gastric surface epithelium changes to sialomucin, but the morphology of the mucosa is unaltered, so that no goblet cells are encountered. The change can, therefore, only be detected by special histochemical stains.

In type III metaplasia (Figure 5b), the mucus component of the epithelium comes to resemble large bowel mucosa. Goblet cells may be present, but contain sulphomucin. This is a highly acidic mucin, which is only weakly periodic acid-Schiff-positive, but may be identified by staining with alcian blue at pH 0.5, or with a high iron diamine technique.

Intestinal metaplasia of all types has a weak association with the presence of gastric cancer. The association is stronger for type III IM (25). The risk is most obvious for distal intestinal type carcinoma and is less for diffuse carcinoma (25, 26). Proximal gastric carcinoma shares many morphological and epidemiological characteristics with carcinoma arising in Barrett's esophagus (27). Although Barrett's esophagus consists of metaplastic epithelium, this is distinct from intestinal metaplasia and does not appear to be related to *H. pylori* infection. Interestingly, when seropositivity for *H. pylori* is compared with the incidence of gastric cancer, the risk is highest for distal intestinal cancer, less for diffuse cancer and least for cardiac cancer (28). This seems reasonable, given that large bowel metaplasia may reasonably be expected to be associated with a large bowel type carcinoma.

Unfortunately, the simple presence of sulphomucin in gastric biopsy material cannot be used as a satisfactory screening method to predict the subsequent development of cancer. This is because it is a relatively frequent finding in individuals with MAG, most of whom will never develop malignancy. It remains to be seen, however, whether the extent of sulphomucin metaplasia could be combined with other risk factors, such as family history, to identify certain high-risk individuals.

**GASTRIC DYSPLASIA**

Dysplasia is a histopathologic diagnosis. The change is neoplastic, but is distinct from reactive hyperplasia and invasive carcinoma. It almost invariably occurs in stomachs affected by atrophic gastritis. For practical purposes, it may be subdivided into high-grade and low-grade. High-grade dysplasia incorporates the term carcinoma-*in-situ*. Morphologically, it is characterized by a high degree of nuclear crowding and enlargement, so that greater than 50 percent of the cell is occupied by nucleus. In low-grade dysplasia, less than 50 percent of the cell volume consists of nucleus. Adenomas of the stomach also contain dysplastic epithelium; however, by convention, use of the term dysplasia
by itself usually implies an ill-defined gross anatomical lesion that is characteristically non-polypoid.

Dysplasia may, however, be visible endoscopically as a change in the texture of the surface mucosa often described as velvety in appearance.

Two morphologically distinct types of gastric dysplasia have been described (29, 30). The commonest, or type I dysplasia, closely resembles the epithelium within an adenoma. The dysplastic cells are crowded with pseudostratified cigar-shaped nuclei and abundant amphophilic cytoplasm (Figure 6). Only small amounts of mucus are present. Type II dysplasia arises in mucosa that may be architecturally abnormal with crowded or branched glands. Both goblet and columnar cells may be seen. The nuclei are enlarged, rounded and vesicular with prominent nucleoli. This form of dysplasia is the most difficult to distinguish from regenerative changes.

The significance of a diagnosis of dysplasia is not fully established (29-33). A major problem is that different investigators have used different criteria for the diagnosis. Not surprisingly, this has produced different results. High-grade dysplasia is the most easy

Figure 5. Intestinal metaplasia. A: Complete metaplasia with goblet cells and absorptive cells. B: Incomplete metaplasia. Both goblet cells and columnar cells contain sulphomucin (high iron diamine stain).
lesion to diagnose, but great care should be exercised in distinguishing it from early invasive carcinoma. The presence of irregularly budding glands or glands with back-to-back formations raise the possibility that early infiltration of the lamina propria may be present. Low-grade dysplasia is easy to confuse with regenerative changes (Figure 6) and has a significant interobserver and intraobserver variability. Low-grade dysplasia is a lesion that may progress, remain the same or even regress (33). High-grade dysplasia is highly significant. Up to 60 percent of cases may have a coincident cancer and a further 25 percent of cases may develop it within 15 months (32). The cancer risk is particularly high when a gross lesion is visualized endoscopically.

At the present time, it is not known what percentage of intestinal carcinomas are preceded by gastric dysplasia, or what is the time interval between the first appearance of dysplasia and the onset of an invasive neoplasm. Most resected carcinomas do not have adjacent dysplasia, suggesting that if originally present, the zone of dysplasia was small and was destroyed by the spreading neoplasm. The management of patients with gastric dysplasia is controversial (33, 34). Most people think that high-grade dysplasia should be treated aggressively. After initial diagnosis, the extent of the lesion should be mapped and all dysplastic areas excised. Mild dysplasia can also be treated in a similar manner (34), but may result in overtreatment of some individuals. For this reason, some groups (33) prefer a more conservative approach, with several follow-up biopsies to confirm that there is a definite persistent abnormality before resection is performed.

Figure 6. Low-grade gastric dysplasia. Pits are lined by cells with hyperchromatic cigar shaped nuclei with loss of polarity.
CONCLUSIONS

1. Currently, the clinicopathological classification of gastritis is unsatisfactory, because the etiology and pathogenesis is not known for many "entities."
2. The histopathological diagnosis of gastritis correlates poorly with endoscopic findings and clinical symptoms.
3. Reactive gastropathy is characterized by increased proliferative activity in the gastric foveolar epithelium. This is a relatively common diagnosis on gastric biopsy and, in many cases, appears to be the result of ingestion of non-steroidal anti-inflammatory drugs.
4. Diffuse superficial gastritis, due to infection by _H. pylori_, is another common cause of gastritis in North America and Western Europe. In most cases, organisms can readily be identified in antral biopsies.
5. Autoimmune gastritis is characterized by a diffuse atrophic gastritis involving the fundus with antral sparing. In the late stages of disease, there may be achlorhydria. Loss of intrinsic factor results in malabsorption of vitamin B12 and pernicious anemia.
6. Multifocal atrophic gastritis is relatively rare in North America, but is much more common in underdeveloped countries. In most instances, this condition is an end stage of _helicobacter_ gastritis, but appears to require other factors (dietary or environmental) for full expression.
7. Both autoimmune gastritis and multifocal atrophic gastritis are characterized histologically by intestinal metaplasia. This is regarded as a precursor of gastric cancer. Unfortunately however, the association is not close enough for the presence of intestinal metaplasia to be used as a screening tool.

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