

MUSINGS OF A GASTROPATH

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The 1980's saw the "discovery" of *Helicobacter pylori* and the realization of the importance of the organism with regards to gastritis. In a manner analogous to the way the discovery of a marker for hepatitis C dramatically increased our understanding of liver disease, the knowledge concerning *Helicobacter* has led to a much greater understanding of the diseases affecting the gastric mucosa. There has been increased interest in processes other than *Helicobacter pylori* affecting the gastric mucosa. We will discuss several of these, including gastritis due to *Helicobacter heilmannii*, lymphocytic gastritis, chemical gastropathy (reactive gastropathy) and, an old "favorite", autoimmune gastritis.

HELICOBACTER HEILMANNII

The gastritis most obviously related to our recognition of *H. pylori* is that due to *H. heilmannii*. As our eyes were trained to recognize *H. pylori*, another larger organism was identified in a much smaller but significant number of cases ("The eye does not see what the mind does not know"). There are over 30 species of *Helicobacter*, including *felis*, *fennelliae*, *cinaedi*, and *heilmannii*. Of these, *H. heilmannii* is the most common, accounting for about 1% of human *Helicobacter* infections. The organism is considerably larger than *H. pylori*, measuring 7 to 10 microns long and up to 1 micron wide. It is tightly spiraled and has terminal flagella. The infection is patchier than that associated with *H. pylori*. There is a tendency for prominent lymphocytic infiltrate of the gastric foveolae. The urease test is frequently positive. There is frequently a history of contact with domestic animals. The majority of cats, dogs and pigs harbor the organism. The exception of pigs, the animals harboring the organism usually show little reaction to it. There does appear to be a significant predisposition to MALT lymphoma.

LYMPHOCYTIC GASTRITIS

Lymphocytic gastritis is characterized by increased numbers of intraepithelial T lymphocytes, typically 25 such cells per 100 epithelial nuclei or greater. Some estimates are that it accounts for about 2% of human gastritis. About 40% are corpus predominant; the remainder are diffuse or antral predominant. There is a clear relationship to celiac disease. It has been estimated that from 10% to 50% of patients with celiac disease have lymphocytic gastritis; it is usually of the diffuse or antral predominant form. There is often a varioliform ("pox-like") appearance. A high percentage of cases not related to celiac disease are thought to be related to prior *Helicobacter pylori* infection, with antibody positivity but no visible organisms. A significant proportion of cases of Menetrier's disease, often with a striking varioliform appearance, have lymphocytic gastritis.

CHEMICAL GASTROPATHY (REACTIVE GASTROPATHY)

Gastric biopsies are frequently done in patients with dyspepsia, or with erosions/ulcers. The endoscopic description of gastritis is usually applied when erythema is noted. Biopsies are taken, and we as pathologists are asked to categorize the type of gastritis. When the typical inflammatory infiltrate of the superficial lamina propria (lymphoplasmacytic with focal clusters of neutrophils) and associated H pylori organisms is found, the diagnosis and subsequent therapeutic course is clear. The next most frequent pattern of damage encountered is that which has been referred to as chemical (reactive) gastropathy (gastritis). The histologic features seen in this condition include the following: foveolar hyperplasia (producing a "villiform" contour); mucosal edema and smooth muscle proliferation expanding the lamina propria; reactive change in the nuclei of the superficial foveolar epithelium; paucity to absence of an inflammatory infiltrate (except when adjacent to erosions/ulcers); and a convoluted contour of the gastric pits. Controversy exists because there is no general agreement as to how many of these findings must be present in order to make the diagnosis, or what the exact criteria are for any of these parameters. As a result there is a lack of intra- and inter-observer consistency in making this diagnosis. Nevertheless, there is great practical importance in separating this form of damage from that of H. pylori, because there are major therapeutic implications. The clinical settings behind chemical gastropathy include bile reflux (in the post-operative state and, less commonly, the intact stomach) and exposure to NSAIDs. Of these, exposure to NSAIDs is by far the most common. It is my personal experience that NSAID related gastropathy tends to produce more prominent fibromuscular proliferation, and reflux results in more prominent convolutions of the foveolae and more prominent reactive nuclear atypia. The fibromuscular response to NSAIDs has been seen in other circumstances of NSAID related damage, such as the "diaphragm" response in proximal small intestine, or the peculiar ileal damage which can mimic Crohn's disease seen in some patients. While there remains considerable frustration in establishing the precise criteria for diagnosing gastropathy, separation from H. pylori gastritis is of considerable practical importance.

AUTOIMMUNE GASTRITIS

Although the features of autoimmune gastritis (frequently related to pernicious anemia) have long been recognized, interest and understanding of H. pylori gastritis have brought them into focus. H. pylori gastritis and chemical gastropathy are antral predominant processes. In contrast, autoimmune gastritis affects the proximal stomach, the area where one finds parietal cells. Parietal cell antibodies are present in 80 to 90% of patients with established pernicious anemia (PA), as are intrinsic factor antibodies in 50-70%. Some patients are detected with antibodies and histologic gastritis prior to the development of anemia. One can raise the question concerning PA – is it a hematologic, gastroenterologic, endocrine or an autoimmune disease? In fact, it is all of these.

Certainly PA will not develop without gastric damage. Patients with PA, and members of their families, are prone to numerous other endocrinologic diseases with an autoimmune etiology. Amongst these one finds diabetes mellitus type I, Addison's disease, hypothyroidism, celiac disease, vitiligo, myasthenia gravis, autoimmune demyelinating disease, and others. The exact incidence of these processes and the manner of inheritance are not known. In the evaluation of gastritis, biopsies should be taken of proximal and distal stomach, and should be labelled as such. Proximal biopsies show loss of parietal cells, atrophy, lymphoid infiltration, intestinal metaplasia, and pancreatic acinar metaplasia. There is frequent hyperplasia of the neuroendocrine elements (ECL cells). The distal (antral) biopsies are usually normal except for prominence of the gastrin producing cells. Hypergastrinemia is usually profound. This results in hyperplasia of the ECL cells, which is the precursor lesion to gastric carcinoids, which occur in about 10% of patients with PA. There is a sequential type of proliferation which occurs in the ECL cells: diffuse, linear, micronodular, adenomatoid, and, finally, "carcinoid". These tumors are the most common type of gastric carcinoid, and tend to be indolent compared to those occurring sporadically or in association with the Zollinger-Ellison syndrome. There is also an increased risk in PA for gastric carcinoma and for esophageal squamous carcinoma. The magnitude of the risk and the frequency of surveillance are controversial.

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