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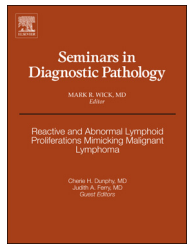

Pathology and differential diagnosis of chronic, noninfectious gastritis

*Alexandros D. Polydorides, MD, PhD**

Departments of Pathology and Medicine (Gastroenterology), Icahn School of Medicine at Mount Sinai, New York, New York

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ABSTRACT

The histologic finding of chronic inflammation in an endoscopic mucosal biopsy of the stomach (chronic gastritis) is very common and usually reflects the presence of *Helicobacter pylori* infection. However, infectious organisms are not always present in biopsy material, and some cases of chronic gastritis do not result from *H. pylori* infection. Thus, the differential diagnosis of this finding is an important one for pathologists to keep in mind. This review presents the three most common and clinically significant causes of chronic, noninfectious gastritis, namely, autoimmune atrophic gastritis, lymphocytic gastritis, and gastric involvement in the setting of inflammatory bowel disease, especially Crohn disease. For each entity, a brief discussion of its etiology and pathogenesis, a review of the clinical and endoscopic features, and a description of the microscopic findings are presented in the context of the differential diagnosis of chronic gastritis with emphasis on helpful histopathologic hints and long-term sequelae.

Introduction

Chronic gastritis: Definition and significance

Chronic gastritis, defined as the presence of a mixed chronic inflammatory infiltrate (mostly lymphocytes and plasma cells) in the lamina propria and occasionally in the epithelium of the stomach, is a common finding in endoscopic mucosal biopsies.[1–9] Most cases are due to infection by *Helicobacter pylori* (and, less often, by its related species *Helicobacter heilmannii*), especially when the chronic inflammation is present as a dense band in the superficial lamina propria accompanied by neutrophilic infiltration of the gastric epithelium. Thus, efforts should be made, including serial sections and special or immunohistochemical stains, to identify the offending agent. However, it is important to note that it is not always possible to identify the organism for various reasons: recent unrelated antibiotic therapy, use of proton pump inhibitors, inadequate sampling, or suboptimal preparation/staining techniques. Furthermore, it is generally accepted that *H. pylori* are rarely found in areas of intestinal metaplasia or near erosions and ulcers, so biopsy specimens that contain these findings might not yield organisms.[10]

If *H. pylori* organisms are not detected after a reasonably exhaustive search, alternative causes of chronic gastritis should be investigated. The goal of this review is to present three groups of diagnostic entities (autoimmune

* *Correspondence address*: Department of Pathology, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1194, New York, NY 10029.
E-mail address: alexandros.polydorides@mountsinai.org

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gastritis, lymphocytic gastritis, and gastric involvement in the setting of inflammatory bowel disease), which are the most common and clinically significant differentials of chronic gastritis when *H. pylori* organisms are not present.[10]

Current recommendations suggest that five biopsies should be obtained during endoscopic evaluation for gastric pathology: two each from the antrum and the corpus/fundus (one each from the greater and lesser curvature, respectively) and one from the lesser curvature at the incisura angularis. The pattern of chronic inflammation (antral-predominant, corpus-predominant, or pangastritis) as well as the presence, extent, and severity of additional findings, such as atrophy, metaplasia, and hyperplasia, are crucial in determining the correct differential diagnosis, as discussed below. Targeted biopsies from the incisura angularis are encouraged because atrophy, intestinal metaplasia, and dysplasia tend to occur in this location first.[11–13]

Gastric atrophy: Definition and patterns

Gastric atrophy is defined as the loss of appropriate (i.e., normal for the anatomic location) gastric glandular epithelial cells.[6,7,14,15] It is more easily and accurately evaluated when lamina propria inflammation is largely resolved. Thus, *H. pylori* eradication and passage of some time for the chronic inflammation to subside are generally required before attempting to assess the extent of atrophy. Atrophic gastritis is characterized by replacement, or loss, of normal glandular elements and expansion of the surrounding lamina propria with fibroblasts and fibrosis and it is almost always accompanied by metaplasia of intestinal, pancreatic acinar, or pseudopyloric types, which may be present singly or in combination. For this reason, atrophic gastritis has been termed metaplastic atrophic gastritis. Two distinct pathogenetic types have been identified: autoimmune (type A) and environmental (type B) atrophic gastritis.

Metaplastic atrophic gastritis due to environmental causes (also called multifocal atrophic gastritis or atrophic pangastritis) usually results from chronic *H. pylori* infection (in more than three quarters of cases). It almost always involves the gastric antrum with variable extension into the proximal stomach. Presumably, prolonged antral inflammation leads to reduced gastric acid production and allows for proximal migration of bacteria to the gastric body, resulting in pangastritis and multifocal atrophic gastritis.

Patients with environmental metaplastic atrophic gastritis do not usually develop achlorhydria or pernicious anemia since the disease does not completely destroy the oxyntic mucosa and a sufficient volume of parietal cells is usually preserved. Thus, patients may develop hypochlorhydria, but usually maintain normal to high-normal serum gastrin levels and do not develop enterochromaffin-like (ECL) cell hyperplasia. Eradication of *H. pylori* infection is not associated with reversal of these histologic findings, but the effect of eradication on gastric carcinoma risk requires further study.[16–19]

Chronic atrophic gastritis: Grading, staging and neoplastic progression

The presence of gastric intestinal metaplasia has been associated with neoplastic progression towards dysplasia and intestinal-type gastric adenocarcinoma.[15,20,21] Although intestinal metaplasia is probably not premalignant (it has been referred to as "paracancerous" rather than "precancerous"), atrophy and intestinal metaplasia signify a mucosa at risk for the development of dysplasia that can progress to carcinoma.[20,21] Conferred risk varies with extent, distribution, and severity of inflammation, atrophy, and metaplasia, but, to date, no specific recommendations or guidelines have been established for the surveillance of patients with these findings. Unfortunately, there are few data describing the extent of cancer risk attributable to intestinal metaplasia, and detection of intestinal metaplasia is limited by sampling errors, which can be substantial when recommended biopsy protocols are not followed.[6]

Several classification systems have been proposed to evaluate and quantify the extent of gastric atrophy.[1,5] Most systems assess the degree of inflammation and extent of atrophy in both the antrum and the body.[6,14,22] It is clear that the pattern of chronic gastritis present and the extent of atrophy are important while identifying gastric mucosa at risk for neoplastic progression. Pathologists may be called upon to provide such information to clinicians in order to facilitate prognostication and management of such patients.[21]

Autoimmune gastritis

Clinical and endoscopic features

Autoimmune gastritis is defined as a corpus-predominant gastritis characterized by chronic inflammation, atrophy of oxyntic glands, and metaplasia, accompanied by the presence of circulating auto-antibodies to parietal cells and/or intrinsic factor, as well as, pernicious anemia in many cases (Fig. 1).[5,7,10] Autoimmune gastritis is relatively uncommon, being present in 2–5% of the population. It is more frequent among elderly women of Northern European descent and shows a predilection for individuals with blood group A. Many affected patients also have other immune-mediated disorders, particularly autoimmune thyroiditis.[23–25] Clinical manifestations are mostly delayed until the loss of a critical mass of parietal cells leads to hypochlorhydria and hypergastrinemia. Reduced gastric acid levels interfere with absorption of non-heme iron, leading to iron deficiency and hypochromic, microcytic anemia in approximately 15% of patients. Patients with severe disease have insufficient parietal cell mass to produce adequate amounts of intrinsic factor and that which is produced may be inactivated by autoantibodies, so these individuals may suffer from vitamin B12 deficiency and megaloblastic anemia. Destruction of chief cells typically accompanies inflammation-mediated destruction of parietal cells and results in reduced levels of pepsin and pepsinogens. There are few distinct endoscopic changes early on in the course of autoimmune gastritis, whereas