Gastritis: a pattern-based approach

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Abstract

Evaluation of inflammatory gastric biopsies is one of the most common tasks pathologists face on a daily basis. Their analysis requires recognition of inflammatory patterns and their associated differential diagnoses, an especially vital skill in the not-so-uncommon instance when there is little clinical information available. In this review we summarize the most common gastric inflammatory patterns and their clinical associations, ranging from Helicobacter gastritis to autoimmune enteropathy to the biopsy with prominent Russell bodies. Our aim is to add to the readers' arsenal of tools to narrow the differential diagnosis in these ubiquitous specimens.

Keywords autoimmune; biopsies; gastritis; patterns of inflammation

Introduction

Evaluation of inflammatory gastric biopsies is one of the most common tasks pathologists face on a daily basis. Their analysis requires recognition of inflammatory patterns and their associated differential diagnoses, an especially vital skill in the not-so-uncommon instance when there is little clinical information available. Pattern recognition is crucial as treatment regimens differ from antibiotics (*e.g. Helicobacter* gastritis) to vitamin supplementation (e.g. autoimmune metaplastic atrophic gastritis [AMAG]) to immunomodulatory therapy (e.g. autoimmune enteritis [AIE]) to dietary modification (e.g. eosinophilic gastritis). Some gastritides are considered benign incidental findings (e.g. Russell body gastritis) with no clinical or treatment consequence, while others are part of a systemic process (e.g. inflammatory bowel disease), and yet others confer an increased risk of lymphoma (e.g. *Helicobacter* gastritis) or carcinoma (e.g. AMAG). Yes, sorting through all these inflammatory patterns can be daunting as there are several entities affecting the stomach and many share overlapping histologic features. In this review we hope to provide the reader with some tools to tease out common inflammatory patterns encountered in daily practice. If we examine these specimens in a consistently systematic fashion we will be able, in the majority of cases, to provide at least a narrow differential for the clinician to work with and effectively guide patient management. The inflammatory patterns presented here are summarized in Table 1.

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The biopsy with chronic inflammation

This general pattern is a common offender and is seen in a myriad of inflammatory (infectious and non-infectious) processes. There are no established criteria for what accounts for "too many" lamina propria lymphocytes and plasma cells. Our approach consists of examining the biopsy at low magnification (4X) searching for increased "dot density" (plasma cells and lymphocytes) in the lamina propria, which separates the glands and imparts a "blue" (hematoxylin) appearance to the biopsy. The next step is to then confirm that the extra "dots" are indeed chronic inflammatory cells at higher magnification (40x) (and not a devious "inflammatory-mimicking" diffuse-type adenocarcinoma). Once we have determined that there is an excess of inflammatory cells, we must pay attention to the distribution of the inflammation in order to narrow the differential diagnosis.

"Top heavy" chronic inflammation

When the majority of the inflammation resides in the upper half of the biopsy (Figure 1), think *Helicobacter* gastritis. *Helicobacter pylori* is a curved flagellated gram negative bacillus strongly associated with gastritis and ulceration. Though *Helicobacter*-associated inflammation most severely affects the antrum,[1] the oxyntic mucosa will display at least mild "top heavy" gastritis.[2] This infiltrate will often be accompanied by at least focal active (neutrophilic) inflammation. "Up front" ancillary stains (Warthin Starry, Giemsa, immunostain) are no longer recommended[3] and instead should be applied to cases with suspicious morphology but where no organisms are seen on H&E. Some cases of *Helicobacter* gastritis feature germinal center formation (A.K.A. follicular gastritis), a finding strongly associated with *Helicobacter* infection.[2] Atrophy and intestinal metaplasia (also known as environmental metaplastic atrophic gastritis [EMAG]) may also be seen. A "bottom heavy" infiltrate in the setting of *Helicobacter* gastritis should trigger suspicion for mucosa associated lymphoid tissue (MALT) lymphoma. These cases will feature dense aggregates of monomorphic lymphocytes with or without perinuclear halos and lymphoepithelial lesions that tend to infiltrate the muscularis mucosae. In these cases, a panel of immunostains is in order; we perform an initial abbreviated version consisting of CD20, CD3, and CD43, and assess for CD20-reactive B cells that aberrantly express CD43. CD3 is necessary because it is normal for T cells to express CD43 and the various stains must be compared. In addition to being a source of gastritis and ulcers, *Helicobacter* gastritis is well-known as a risk factor for the development of gastric carcinoma. *Helicobacter heilmannii* is a rare (<1% of cases), longer and more tightly coiled variant (Figure 2) that cross-reacts with *H. pylori* on immunohistochemistry. The gastritis associated with *H. heilmannii* has the same features as that of *H. pylori* but the inflammation is typically less severe.

"Bottom heavy" chronic inflammation

A number of gastritides may be associated with a "bottom heavy" type of inflammation. The inflammatory pattern associated with AMAG, most commonly seen in females in their 6th decade, is important to identify as it leads to pernicious anemia due to vitamin B12 deficiency and confers a roughly 3 fold increased risk of gastric carcinoma. Patients may present with

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Differential diagnosis for each histologic pattern

The Biopsy with Chronic Inflammation
- "Top Heavy" distribution
  - Helicobacter gastritis (*H. pylori* or *H. heilmanni*)
- "Bottom Heavy" Distribution
  - Autoimmune metaplastic atrophic gastritis
  - Autoimmune pangastritis
  - Autoimmune enteritis
- Patchy Distribution
  - Inflammatory bowel disease

The Biopsy with Chronic Active Gastritis without *Helicobacter pylori*
- Treated *Helicobacter* infection (typically no activity)
- Inflammatory bowel disease

Chemical/Reactive Gastropathy Pattern
- Non-steroidal anti-inflammatory drugs
- Bile reflux
- Antral biopsy of autoimmune metaplastic atrophic gastritis
- Gastric antral vascular ectasia (GAVE)

The Biopsy with Prominent Eosinophils
- Helicobacter Gastritis (H. Pylori or H. Heilmanni)
- Autoimmune metaplastic atrophic gastritis
- Post-radiation
- Parasite
- Solid organ transplantation
- Collagenous gastritis
- Inflammatory bowel disease
- Eosinophilic gastritis
- Medications

The biopsies with Lymphocytic or Collagenous Patterns
- Helicobacter Gastritis (H. pylori or H. heilmanni)
- Celiac disease
- Medications

The Biopsy with Prominent Mott Cells
- Russell body gastritis

The Biopsy with a Prominent Monocytic Reaction
- Cytomegalovirus
- Epstein–Barr virus

Table 1

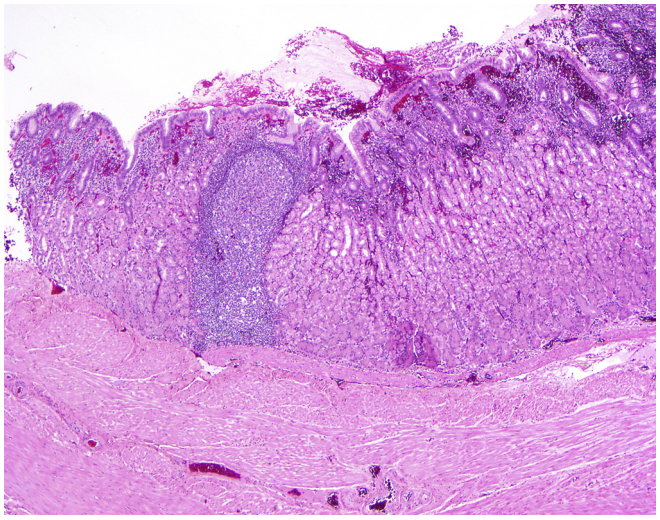

Figure 1 *Helicobacter gastritis*. Note the superficial ("top heavy") lamina propria inflammation. This field also shows a prominent lymphoid aggregate with germinal center formation, another clue to the diagnosis.

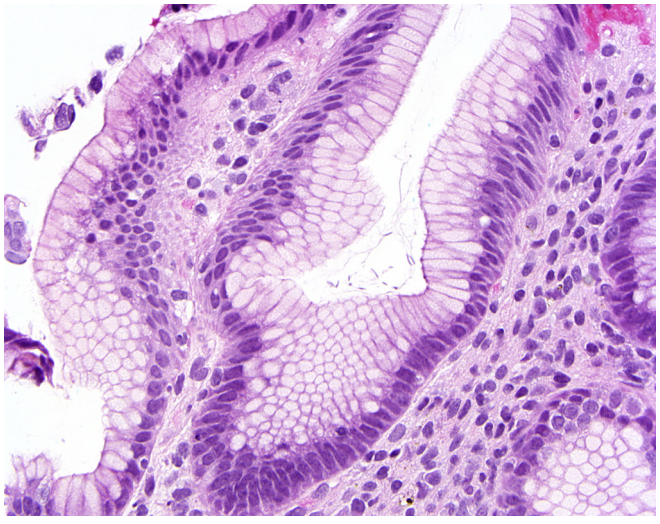

Figure 2 *Helicobacter heilmanii*. *H. heilmanii* is longer and more tightly coiled than *H. pylori*.

iron deficiency anemia as acid is necessary for iron absorption. The histologic changes of AMAG are **limited to the gastric body**. Biopsies from the antrum will be normal or present a reactive/chemical gastropathy pattern (discussed later). Besides "bottom heavy" chronic inflammation, the gastric body will feature atrophy with injured, decreased or absent parietal cells, intestinal metaplasia, and enterochromaffin cell like (ECL) cell hyperplasia (Figures 3 and 4). Roughly half of the cases will show pancreatic metaplasia, a finding rarely seen in the stomach outside the setting of AMAG.[4] Interestingly, the amount of inflammation tends to decrease as atrophy develops and the parietal cells are lost (a distinguishing feature with autoimmune pangastritis, discussed later). The findings can be patchy with some areas of the stomach showing full blown atrophy and others showing preserved oxyntic mucosa. Immunohistochemistry can be useful when the specific source of the biopsy (antrum vs. body) is in question. Atrophic (antralized) oxyntic mucosa will be negative for gastrin (or may have few gastrin-immunoreactive cells) as it lacks G cells (only present in the "true" antrum).

In its early stages ("early AMAG"), this process can be challenging to recognize as it can feature mild to severe full thickness or deep chronic inflammation of the gastric body accompanied by subtle or focal findings such as inflammatory destruction of oxyntic glands, intestinal, pyloric, or pancreatic acinar metaplasia, prominent lamina propria eosinophils, and parietal cell pseudohypertrophy.[5] The AMAG biopsy (early or fully developed) will feature linear and/or nodular ECL cell hyperplasia, which can occasionally be seen on H&E but is better highlighted on a chromogranin or synaptophysin immunostain. Multiple types of polyps are common in the setting of AMAG including hyperplastic polyps, type 1 gastric neuroendocrine tumors (carcinoid tumor, which are indolent), and intestinal or pyloric

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