

Peer Review File

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REVIEWER A

Comment 1: One suggestion is to either have a summary table or a diagnostic-approach algorithm to consolidate the data in the paper. This will provide a form of quick-reference to help with decision making for the busy clinician.

Reply 1: Thank you for the excellent suggestion. A summary table (Table 1) has been added in the Summary portion of the manuscript (page 28, line 596).

Changes in the text: Table 1 summarizes key histologic features and helpful stains for various types of gastritis and gastropathy.

REVIEWER B

Comment 1: Page 5, line 94. Introduces the terms gastritis and gastropathy, however, the difference between these 2 terms is not defined. I would suggest adding a one-sentence definition for each term at this point in the manuscript.

Reply 1: Thank you for the excellent suggestion. We have added two sentences to define these terms and their difference at the beginning of the 4th paragraph in Introduction.

Changes in the text: On page 6, lines 98-100, the following two sentences are added: “Gastritis and gastropathy differ mainly based on the presence or absence of inflammation associated with mucosal injury. In contrast to the presence of inflammatory cell infiltrates seen in gastritis, gastropathy is defined by mucosal damage with minimal or no inflammation.”

Comment 2: Page 9, line 198. Mentions transmural necrosis in gastrectomy specimens in the setting of histopathological findings in Sarcina infection. The presence of organisms in this setting is likely to be a secondary phenomenon.

Reply 2: Thank you for the excellent suggestion. We have included phrasing in this sentence to note that this is likely a secondary feature.

Changes in the text: Page 11, lines 214-216, the sentence has been changed to: “Transmural necrosis can be seen in gastrectomy specimens, but the presence of organisms in this setting is likely a secondary and incidental finding.”

Comment 3: Page 11, line 230. “Marsh lesions” is a little obscure. Perhaps change this to “exclude histological features of celiac disease.”

Reply 3: Thank you for the excellent suggestion. The phrase “Marsh lesions” is now replaced by the suggested phrasing.

Changes in the text: Page 12, lines 245-247, the sentence has been changed to: “Therefore, the presence of antral-predominant LG may suggest the need for additional serologic testing for celiac disease and duodenal biopsy to exclude histologic features of celiac disease.”

Comment 4: Page 11, lines 238-240. Given that it is topical, and we are beginning to see a lot of it, it is probably worth including immune checkpoint inhibitors in the list of causes of lymphocytic gastritis.

Reply 4: Thank you for the excellent suggestion. Immune checkpoint inhibitors are added to this list. In addition, the association of lymphocytic gastritis with immune checkpoint inhibitors has also mentioned under “Gastropathies associated with chemotherapeutic and radiation therapies” (page 25, lines 535-539).

Changes in the text: Page 13, lines 256-258. The sentence has been changed to: “Other associations with LG include human immunodeficiency virus (HIV) infection, common variable immunodeficiency (CVID), Crohn disease, lymphocytic enterocolitis, medications (including immune checkpoint inhibitors), and gastric lymphoma (35, 43-45).”

Comment 5: Page 15, lines 286-291. Common variable immunodeficiency is also worth including in the list of associations of collagenous gastritis.

Reply 5: Thank you for the excellent suggestion. Common variable immunodeficiency is now included in this list.

Changes in the text: Page 15, lines 305-307: The sentence has been changed to: “Other clinical associations include Hashimoto thyroiditis (52), Sjögren syndrome (60), CVID, and polymyositis (52).”

Comment 6: At the end of the section on reactive gastropathy there is a lead into a discussion of depositions (iron, calcium, lanthanum, resins). This seems a little out of place and I would prefer to see these listed under a new heading (e.g. gastropathies associated with tissue deposition). As described in the text many of these do not show a well-developed reactive gastropathy pattern.

Reply 6: Thank you for the excellent suggestion. We have grouped these paragraphs under the suggested header “Gastropathies associated with tissue deposition” and also added additional headers for the paragraphs relating to chemotherapy and radiation associated changes (“Gastropathies associated with chemotherapeutic and radiation therapies”) and for portal hypertensive gastropathy and gastric antral vascular ectasia.

Changes in the text: Three new headers are added: Page 23, line 484: “Gastropathies associated with tissue deposition”; page 25, line 529: “Gastropathies associated with chemotherapeutic and radiation therapies”; page 26, line 548: “Portal hypertensive gastropathy and gastric antral vascular ectasia”.

Comment 7: Page 25, line 565 and page 26, line 566. Russell is spelled incorrectly (it should have 2 l's).

Reply 7: We apologize for this oversight. The spelling for “Russell” has been corrected in both places.

Changes in the text: Page 27, lines 586 and 587: “Russel” is changed to “Russell”.

REVIEWER C

Comment 1: Abstract-section

The text under ‘Key content and Findings’: I disagree that clinical information is not that important, which is now suggested “the clinical presentations, endoscopic findings and

laboratory result lack diagnostic specificity in general”. Information such as, is *H pylori* (recently) treated, does the patient has any medication (especially NSAID, iron pills, antibiotics, immunotherapy, and PPIs), and what is the endoscopic image and location in the stomach of the biopsies taken, are all very important and may lead together with the histology to the correct diagnosis. Examples are: Menetrier’s disease (if you are not informed about the endoscopic findings, the location of the biopsies and e.g. the laboratory findings, it will be impossible to even suggest the diagnosis), same holds true for immunotherapy associated gastritis and IBD. I think in general a good understanding, good communication with your endoscopists/ clinical colleagues is very important in gastritis pattern recognition. Also for GAVE and portal gastropathy, there is not really a histopathologic pattern, but in combination with clinical information, this diagnosis can be made, as is also mentioned later on in the review.

Reply 1: We completely agree with the reviewer. We have modified the language in this sentence to reflect the importance of clinical, endoscopic, and laboratory correlation with histopathologic findings. We have also added a few sentences about clinical and endoscopic correlation in the introduction (please also see reply to comment 2 below).

Changes in the text: Page 2, lines 33-36: The sentence has been changed to: “The correct diagnosis of various types of gastritis and gastropathy rests primarily on histopathologic evaluation of endoscopic biopsies of the gastric mucosa and should always be taken in the context of clinical presentations, endoscopic findings, and laboratory results.”

Comment 2: Introduction

Clear overview of antrum and oxyntic gastric mucosa. Why is gastric cardia histology not briefly introduced?

Again, the statement that clinical presentation is not important, needs a bit more explanation, with examples that it is important for some specific diagnoses. See above.

Reply 2: Thank you for the excellent suggestion. We have added a few sentences to describe gastric cardia histology. We have also corrected the statement about the importance of clinical presentation. We completely agree that clinical and endoscopic correlation is an essential part to histologic evaluation (please also see our reply to comment 1 above).

Changes in the text: Page 4, lines 59-62: The following sentences are added: “The mucosa lining the gastric cardia is somewhat similar to antral mucosa but does not contain G cells. The glands in cardiac mucosa can be entirely mucinous or composed of a mixture of mucinous and oxyntic glands (cardio-oxyntic mucosa). Mild cystic dilation of the mucinous glands is a common finding in cardiac mucosa.” Page 6, lines 100-109: The following sentences are added or modified: “The correct diagnosis of various types of gastritis and gastropathy rests primarily on histopathologic evaluation of endoscopic biopsies of the gastric mucosa, but these findings should always be taken in the context of clinical presentations, endoscopic findings, and laboratory results. Relevant clinical information, such as knowing whether the patient has been treated for *H. pylori* or has taken specific medications (i.e. NSAIDs, iron pills, immunotherapy, or antibiotics, etc.), provides invaluable information for the histopathologic diagnosis. The endoscopic impression and labeled biopsy location of the specimen are also crucial items that should always be evaluated concurrently with histology. An accurate histopathologic diagnosis can only be obtained with a good understanding of the clinical and endoscopic picture.”

Comment 3: Line 127: misses the word “the” before “majority”.

Reply 3: We apologize for this oversight. We have modified this sentence to sound more concise and less convoluted. Additionally, the word “the” has been added before “majority” at another place (page 7, line 128).

Changes in the text: Page 8, lines 140-142: The sentence has been modified: “In most cases, *H. pylori* organisms can be visualized on routine H&E stain as slender, slightly curved or curvilinear rods in the mucin on the mucosal surface and in the gastric pits (Figure 4B).”

Comment 4: Line 140: difficult to read, is the last part “does not eliminate the bacteria” only referring to PPI therapy or also antibiotics? Maybe rephrase.

Reply 4: It is our understanding that both antibiotics and PPI can suppress but may not be able to entirely eliminate the organisms. The sentence has been slightly modified in an attempt to avoid confusion.

Changes in the text: Pages 8, lines 152-154: The sentence has been slightly modified: “Immunohistochemistry is more sensitive than special stains in detecting *H. pylori* and is useful when the organisms are sparse following antibiotic and/or proton pump inhibitor (PPI) therapies that may substantially suppress but do not entirely eliminate the organisms (12).”

Comment 5: Line 231: HP is also associated with LG, is also in line 221. I think the entire Alinea of 231-237 is a bit unnecessary here. Just the notion that is may be related to HP/ HP should be excluded in LG, should be enough.

Reply 5: We chose to discuss LG’s association with celiac disease and HP in separate paragraphs. We agree that the introductory sentences for both paragraphs appear redundant and have rephrased both sentences to diminish the redundancy. In the paragraph about HP and LG, we wanted to emphasize that the absence of organisms does not entirely exclude *Helicobacter* infection given the discordance between positive serology and negative histology. We hope that the reviewer would agree with us in this regard.

Changes in the text: Slight modifications are made in the two paragraphs discussing LG’s association with celiac disease (page 12, lines 238-247) and *H. pylori* (page 13, lines 248-255).

Comment 6: Line 240: what is meant by varioliform gastritis, that is rather a pattern description than a diagnosis, so I would not mention it here.

Reply 6: We agree with the reviewer. The phrase “varioliform gastritis” has been removed.

Changes in the text: Page 13, lines 256-258: The sentence has been changed to: “Other associations with LG include human immunodeficiency virus (HIV) infection, common variable immunodeficiency (CVID), Crohn disease, lymphocytic enterocolitis, medications (including immune checkpoint inhibitors), and gastric lymphoma (35, 43-45).”

Comment 7: Methods are missing, no information on the process of literature selection. It is not really a problem for this narrative review, but maybe a small Alinea/statement what the methods were/ which literature was selected.

Reply 7: Thank you for the suggestion. We have modified the sentence in the methods to be more specific.

Changes in the text: Page 2, lines 31-32: The sentence has been modified: “**Methods:** A comprehensive literature review was conducted on PubMed, and personal practice experience was incorporated.”

Comment 8: Also it is unclear how the selection of the diagnoses to include in this review was made. Why not include several medication-gastritis patterns, such as specific antibiotics, immunotherapy etc. And same for Menetrier's disease and other rare gastropathy disorders. Currently, patterns and diagnoses are mixed up in the literature review, I would suggest to make a overview table with patterns and the diagnoses included under each pattern, so that it gives a practical tool for pathologists to use.

Reply 8: Thank you for the excellent question. We have selected the most common patterns of injury and diagnoses that pathologists typically encounter on surgical pathology. Please see the last paragraph of Introduction (page 7, lines 116-120): “In this article, we focus on the histopathologic features that are essential to the recognition of most common types of chronic gastritis. A few uncommon types of non-*Helicobacter* infectious gastritis are also discussed. In addition, histopathologic features of reactive gastropathy, which usually shows no or minimal inflammation but are frequently encountered in daily practice, are described.” We chose to omit the more esoteric entities for this review.

An overview table (Table 1) with all the discussed patterns of injury/diagnoses has been added.

Changes in the text: Please see Table 1.