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Review Article

American Registry of Pathology Expert Opinions: Evaluation and reporting of biopsies from the columnar-lined esophagus and gastro-esophageal junction (GEJ)☆

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ABSTRACT

This review is part of a collaboration between the American Registry of Pathology (the publisher of the Armed Forces Institute of Pathology Fascicles) and Annals of Diagnostic Pathology. It is in a series of expert recommendations on topics encountered in daily practice. The authors, two pathologists and a gastroenterologist, met on 19 January 2019 tasked with developing expert recommendations on reporting biopsies from the columnar lined esophagus and gastroesophageal junction. Our opinions for reporting revolve around noting the presence and absence of goblet cells and clues for confirming whether a sample is from the tubular esophagus. We also illustrate congeners of goblet cell. We present the information in the form of questions and answers.

Evaluating for Barrett esophagus and the neoplasia associated with it is a significant part of the practice of Western pathologists [1]. Columnar metaplasia in the esophagus is the source of anxiety for patients and pathologists alike. This topic is approached using a series of frequently asked questions (FAQs). In this review, squamous lesions (reflux esophageal changes, eosinophilic esophagitis, lymphocytic esophagitis, esophagitis from infectious causes) are not discussed but a discussion of reporting the latter is planned as a later expert recommendations topic.

1. FAQ: what information is ideally supplied by the endoscopist?

Answer:

1. Location of the biopsies (GEJ or top of the gastric folds, esophagus] distal, mid, proximal, if relevant, as per eosinophilic esophagitis], squamocolumnar junction or Z line). It is acceptable for the endoscopist to designate the biopsy site by centimeters as well as the anatomic site but she should avoid designating the location in centimeters only.
2. If biopsies are from a visible lesion, they should be designated as such, otherwise, the pathologist should assume random sampling. However, we would caution that some subtle alterations are not detected by all endoscopists.
3. Whether the sample is from a patient who has undergone ablation and whether the sample is from a neoZ line if so.

Examples of well-designated biopsies:
"distal esophagus, 33 cm"
"GEJ, neo-Z line"
Examples of poorly designated biopsies:
"34 cm"
"Doe, John"

2. FAQ: how does Barrett's esophagus appear endoscopically?

Answer:

Barrett's esophagus appears as velvety "salmon pink colored" epithelium that extends as "tongues" or circumferentially replaces whitish squamous mucosa above the gastric folds. When an area of Barrett's esophagus is encircled by squamous mucosa, the encircled zone is referred to as an "island".

Endoscopy colleagues use a system to describe the extent of Barrett's esophagus called the Prague system in which the distance of the circumferential length of Barrett's esophagus is recorded ("C") and the maximum length is recorded as well ("M") [2]. This method is simple for endoscopists to use and has allowed standardization of endoscopy

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reports. When C&M data are provided to pathologists, they can help pathologists understand whether the samples are from long segment or short segment Barrett's esophagus – long segment means >3 cm.

In patients who have undergone endoscopic therapy with endoscopic mucosal resection (EMR) or ablation, the Prague classification does not apply. Residual intestinal metaplasia in the tubular esophagus may be described as Prague C0M0 if only "islands" of Barrett's esophagus remain, but this does not mean that the patient does not have Barrett's esophagus [3]. This is limitation of the Prague classification.

Additionally, some patients have inlet patches. Inlet patches, found in both adults and children are believed to be embryologic vestiges from early gestation when the esophagus is lined by columnar epithelium. They are identified in about 1% of patients undergoing upper endoscopy [4]. Inlet patches manifest in the cervical esophagus and are generally asymptomatic. However, there are occasional complications in the form of local injury (webs, strictures, ulcers, and fistulas) that can result in symptoms. For example, some patients suffer severe hoarseness from reflux into the larynx that can require ablation of the inlet patch.

Endoscopically, they present as oval or round smooth patches that extend longitudinally [4], cervical esophageal nodules, or salmon colored mucosa of the cervical esophagus [5].

3. FAQ: what elements should the report by the pathologist contain for biopsies of the esophagus and gastroesophageal junction?

Answer:

1. Whatever types of epithelium are present in the sample should be reported (squamous, gastric [without oxyntic cells], oxyntic [corpus \body type], columnar mucosa with intestinal metaplasia). All types seen should be mentioned.
2. Any squamocolumnar transition (and the type, cardia/corpus/both) included in the biopsy
3. If columnar epithelium is present, the presence or absence of intestinal metaplasia.
4. Report any subsquamous (buried) intestinal metaplasia [6].
5. If columnar epithelium with intestinal metaplasia is present, the presence or absence of dysplasia.
6. If dysplasia is present, it should be reported and graded regardless of whether goblet cells are seen (not the focus of this discussion).
7. Squamous dysplasia/intra-epithelial neoplasia should be reported but is not the focus of this short discussion.
8. Inflammatory lesions of squamous mucosa should be reported but are not further addressed here.

Figs. 1–3 show examples of the endoscopic appearances and the tandem biopsy findings from several patients with suggested pathology reports for them.

3.1. FAQ: what are some histologic clues that a sample showing columnar epithelium has been taken from the tubular esophagus when the information has not been provided.

Finding squamous epithelium is a terrific clue that a sample is from the GEJ but does not prove that a sample of columnar epithelium included in the biopsy is from the tubular esophagus itself. On the other hand, finding esophageal ducts or submucosal glands proves that a sample is from the tubular esophagus [7] (Figs. 4–5).

4. FAQ: how is Barrett's esophagus defined?

Answer: It varies geographically. In the United Kingdom and Japan the definition differs from that in the United States.

British (and Japanese) definition of Barrett's esophagus 2014:

- Columnar epithelium with or without goblet cells extending ≥1 cm above the gastric folds [8]

American Gastroenterological Association definition of Barrett's esophagus 2011:

- Columnar epithelium in the esophagus that contains goblet cells – no length requirement [9]

American College of Gastroenterologists' definition of Barrett's esophagus 2016:

- Columnar epithelium with goblet cells extending ≥1 cm above the top of the gastric folds [10]

The last definition (the 2016 one from the American College of Gastroenterologists) can be a challenge for pathologists. Whereas sometimes, the length of a segment of columnar epithelium is provided to the pathologist, in other instances, the only available information is that the sample is labeled "esophagus". Obviously if there are samples labeled "esophagus, 40 cm" with intestinal metaplasia and samples labeled "esophagus, 34 cm" with intestinal metaplasia, the affected segment of lesion measures at least 1 cm. The American College of Gastroenterology suggested the term "specialized intestinal metaplasia

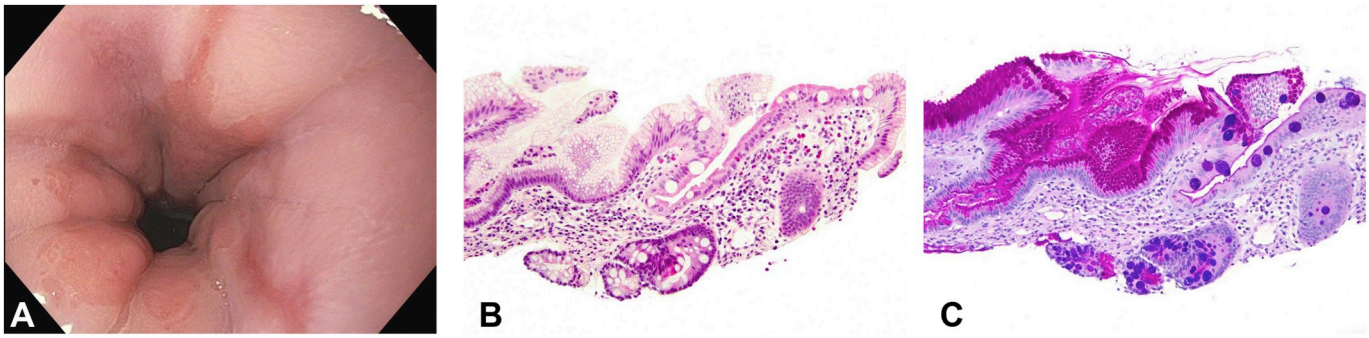

Fig. 1. A. Endoscopic image from a patient with erosive esophagitis showing an irregular squamocolumnar junction with ultrashort columnar tongues <1 cm in length and short linear erosion at the 5 o'clock position (Los Angeles Grade A mild esophagitis). Biopsies from the gastroesophageal junction showed intestinal metaplasia. This would not be consistent with a diagnosis of Barrett's esophagus using American College of Gastroenterology (ACG) definition, but potentially consistent with the definition by the American Gastroenterological Association (AGA) and British Society of Gastroenterology (BSG). Two sets of follow-up endoscopy and biopsies did not show Barrett's esophagus. B. The hematoxylin and eosin (H&E) shows cardiac type mucosa with intestinal metaplasia and well as squamous mucosa with reactive changes. SUGGESTED REPORT: GE JUNCTION, 38CM (BIOPSY): CARDIAC-TYPE MUCOSA WITH FOCAL INTESTINAL METAPLASIA. ADJOINING SQUAMOUS MUCOSA WITH REACTIVE EPITHELIAL CHANGES. C. A periodic acid Schiff/ Alcian blue (PAS/AB) stain was done in this case (such staining is not necessary) and shows complete intestinal metaplasia. This indicates that there are goblet cells adjoining completely intestinalized cells with a brush border. This is a clue that the intestinal metaplasia is from the stomach rather than the esophagus but only a clue. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

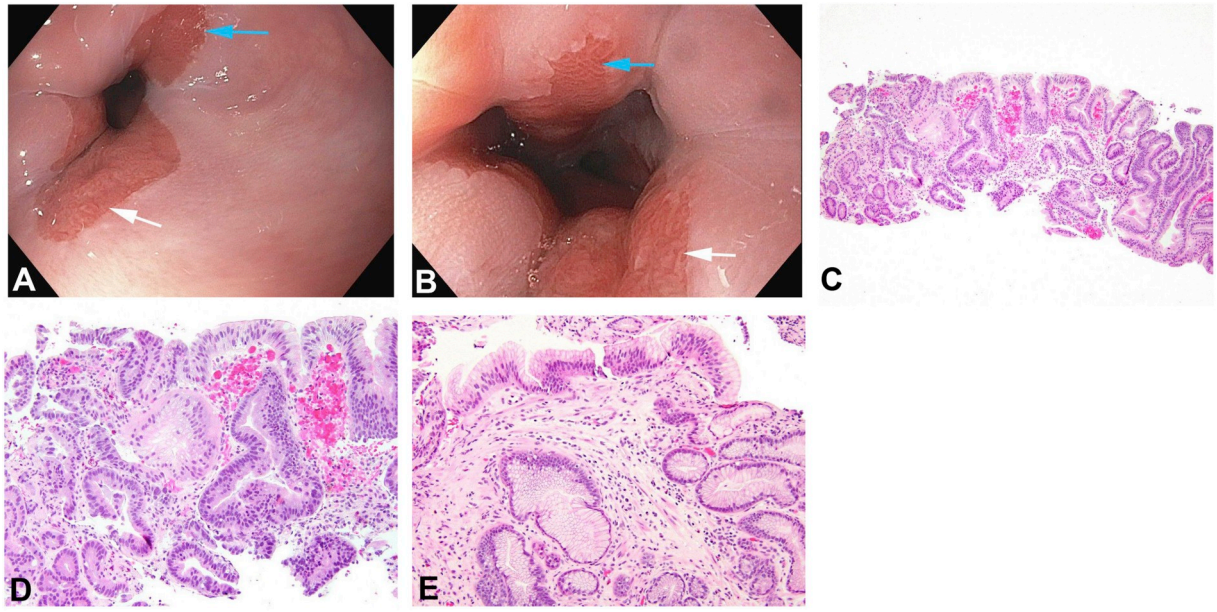

Fig. 2. A and B. Endoscopic high resolution white light images from a patient with "short" 1 cm columnar tongue (Prague class C0M1). Targeted biopsies showed Barrett's esophagus with high grade dysplasia (HGD) and low grade dysplasia (LGD) localized to the columnar tongue on the anterior wall (blue arrows). Biopsies from the opposite columnar mucosa (< 1 cm) show cardiac mucosa (white arrows). C. This sample is from the indicated area in Fig. 2A and B. The tissue is fragmented but dysplastic. SUGGESTED REPORT: ESOPHAGUS, "ANTERIOR TONGUE, " 41 CM (BIOPSY): HIGH GRADE DYSPLASIA IN BARRETT'S ESOPHAGUS. Goblet cells are not seen in this image but were present in the sample. When they are absent, it is acceptable to report "columnar epithelial dysplasia". D. This sample is from the other indicated area in Fig. 2A and B. There is only cardiac type mucosa. SUGGESTED REPORT: ESOPHAGUS, POSTERIOR TONGUE, 41 CM (BIOPSY): CARDIAC-TYPE MUCOSA WITH CHRONIC INFLAMMATION. NO GOBLET CELLS CHARACTERISTIC OF BARRETT'S ESOPHAGUS ARE SEEN. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

of the esophagogastric junction" for lesions that contain goblet cells but do not satisfy the length requirement for the mucosal irregularity [10].

However, we would point out that the key issue is to avoid diagnosing Barrett's esophagus when the patient simply has intestinal metaplasia of the gastric cardia since the consequences include patient anxiety, increased insurance fees, and excessive surveillance. In reality, many colleagues continue to use the AGA criteria for Barrett's esophagus, for which there is no length requirement, to decide whether to perform surveillance. Below are sample notes that can be used. Either type of report is acceptable and should reflect local practice.

5. Sample reports and notes using ACG criteria:

5.1. Situation A – biopsy labeled "esophagus"

Barrett's esophagus, negative for dysplasia. See note.

Note: The above diagnosis of Barrett esophagus is made due to presence of goblet cells (intestinal metaplasia) with the assumption that the biopsies were obtained from columnar mucosa in the distal esophagus. In addition, the 2016 American College of Gastroenterology (ACG) guidelines advocate that the mucosal irregularity must extend at least 1 cm above the top of the gastric folds.

Reference: Shaheen NJ, Falk GW, Iyer PG, Gerson LB; American College of Gastroenterology. ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus. Am J Gastroenterol. 2016 Jan;111 [1]:30–50

5.2. Situation B – biopsy labeled "gastro-esophageal junction"

Cardiac mucosa with intestinal metaplasia. See note.

Note: This biopsy shows gastric-type mucosa with scattered goblet cells. The diagnosis in this case depends on the location of this biopsy. If the metaplasia is in the tubular esophagus and a mucosal irregularity is noted that extends at least 1 cm above the top of the gastric folds, the findings are consistent with Barrett's esophagus. If the GEJ and SCJ are coincident the findings are diagnostic of intestinal metaplasia of the gastric cardia.

Reference: Shaheen NJ, Falk GW, Iyer PG, Gerson LB; American College of Gastroenterology. ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus. Am J Gastroenterol. 2016 Jan;111 [1]:30-50

6. FAQ: The ACG 2016 criteria state: *BE should be diagnosed when there is extension of salmon-colored mucosa into the tubular esophagus extending ≥ 1 cm above the top of the gastric folds with biopsy confirmation of IM (strong recommendation, low level of evidence)*. If there is a 0.5 cm island that is >1 cm above the top of the gastric folds that contains intestinal metaplasia, is it Barrett's esophagus?

Answer: Yes. The ≥1 cm length of mucosal irregularity rule was created to separate irregular Z lines with intestinal metaplasia in cardiac mucosa from true Barrett's esophagus, which is a lesion of the tubular esophagus. By the rules of the ACG, the described 0.5 cm island >1 cm above the top of the gastric folds is "intestinal metaplasia in the esophagus" and not Barrett's mucosa. As noted above, this is a shortcoming of the Prague classification [3]. By common sense, such an island is biologically Barrett's esophagus but it is not formally recognized as such according to the Prague classification. However, recent data indicate that such a lesion should be managed as per Barrett's esophagus [3]. Another point worth reiterating here is that identifying esophageal ducts or submucosal glands associated with any type of columnar epithelium (whether cardiac, cardio-oxyntic, or epithelium with intestinal metaplasia) proves that the columnar epithelium is from the esophagus. As such, it can be of value to report the presence of esophageal ducts or glands to confirm that the sample is truly from the esophagus (Figs. 4-5) [7].

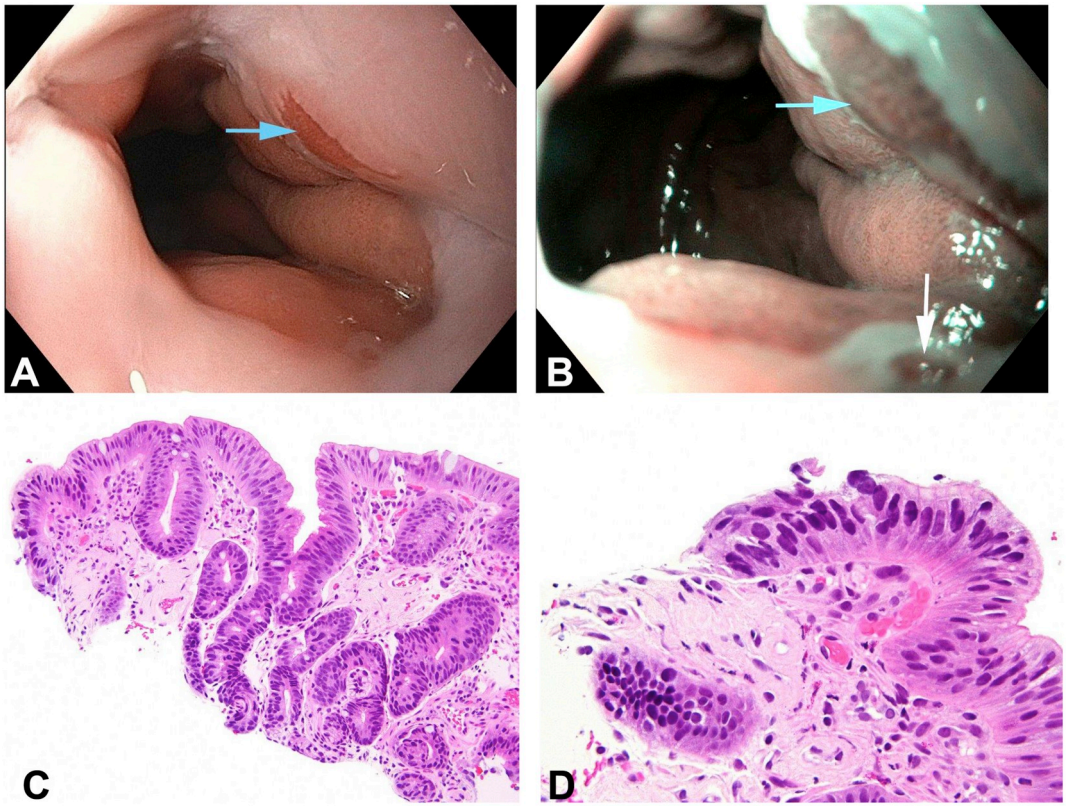

Fig. 3. A. and B. This patient was referred for BE HGD in biopsies from the gastroesophageal junction (GEJ), confirmed upon review of outside biopsies. Endoscopic images (high resolution white light (A), narrow band imaging (B) from baseline mapping EGD at JHH showed two columnar islands above the GEJ. The blue arrow (A and B) indicates the island with HGD, the white arrow (B) shows the island without IM (cardiac mucosa, not BE). Biopsies from the GEJ showed "Barrett's esophagus". In this patient, the IM at the GEJ is true BE. The BE Prague classification is C0M0 (no tongues or circumferential BE) as the squamocolumnar junction coincides with the GEJ, demonstrating the limitation of the Prague classification. C. This sample shows dysplasia in Barrett's esophagus. Much of the process appears low grade but there is surface loss of nuclear polarity at the left. D. This is a high magnification of the image seen in Fig. 3C. Note the nuclear hyperechromasia. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

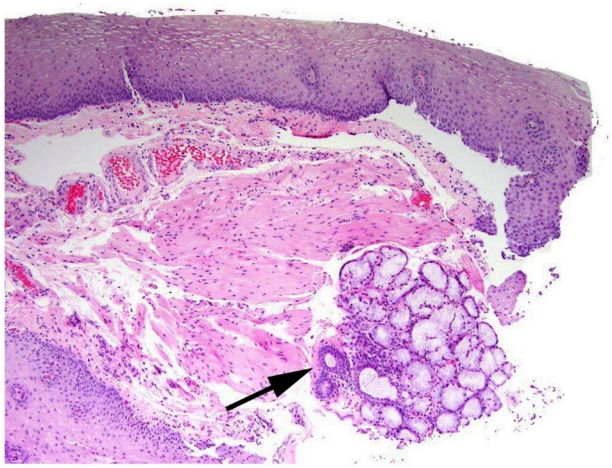

Fig. 4. Although the presence of squamous epithelium suggests that the sample was obtained from the esophagus, it does not exclude a gastroesphageal location. However, this image shows both submucosal glands and a duct (indicated), findings that tell us that the sample is from the tubular esophagus.

7. FAQ: why do some observers want to eliminate the requirement for goblet cells for a diagnosis of Barrett's mucosa?

Answer:

Some studies suggest that most esophageal adenocarcinomas that are detected arise in the absence of intestinal metaplasia. In one of them, for example, the authors evaluated endoscopic mucosal resection samples and found adjoining intestinal metaplasia in less than half of the samples with early cancers [11]. However, these authors did not attempt to learn if the patients had separate or prior samples that contained intestinal metaplasia. It is known that the likelihood of finding goblet cells is a function of both the length of the Barrett's esophagus segment and the rigor of the biopsy protocol – taking biopsies according to guidelines increases the likelihood of finding them [12]. Additionally, goblet cell density is a function of intraluminal pH (the more the acid the greater the density of goblet cells) [13] but it diminishes with progression to adenocarcinoma [14]. This would account for a paucity of goblet cells surrounding the early carcinomas described above [11].

In two West Coast US studies, intestinal metaplasia essentially always accompanied high grade columnar epithelial dysplasia and carcinomas [15,16]. We found similar results in an East Coast study [17]. We would endorse retaining the requirement for goblet cells but others have suggested eliminating the requirement [18]. Regardless, there is a subset of esophageal adenocarcinomas that is unassociated with intestinal metaplasia but they are not numerous (about 10% in our material [17]) and it is virtually impossible to rule out the possibility that the background goblet cells have been overrun by the neoplastic proliferation. Until robust prospective studies confirm a significant risk of subsequent neoplasia in patients without intestinal metaplasia eliminating the requirement for goblet cells to diagnose Barrett's esophagus in the United States will only serve to further reduce the cost effectiveness of surveillance in these patients.

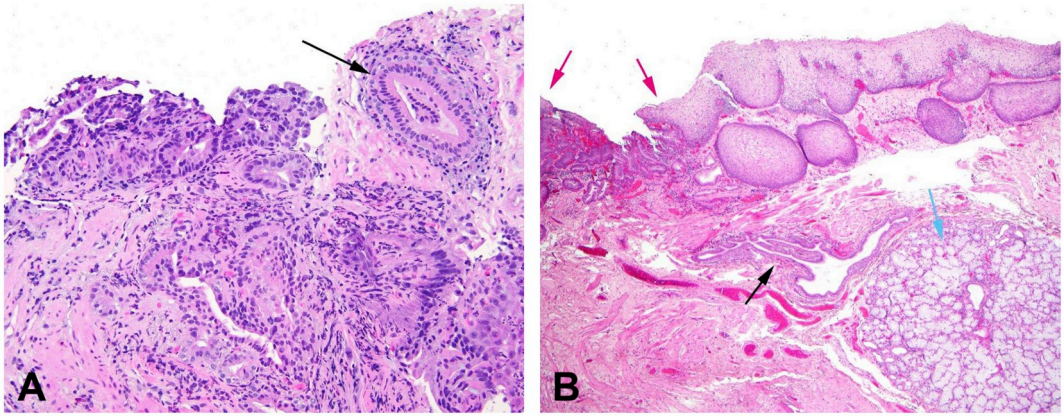

Fig. 5. A. This example of high grade columnar epithelial dysplasia was labeled “44 cm” without other qualification. The presence of the esophageal duct (indicated) confirms that the lesion arose in the esosphagus. B. In this sample, columnar epithelium without goblet cells is flanked by squamous epithelium (pink arrows), which suggests that this columnar epithelium is in the esophagus but does not exclude a gastroesophageal junctional location. However, the presence of the duct (black arrow) and submucosal gland (white arrow) supports that the columnar epithelium is metaplastic and in the tubular esophagus. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

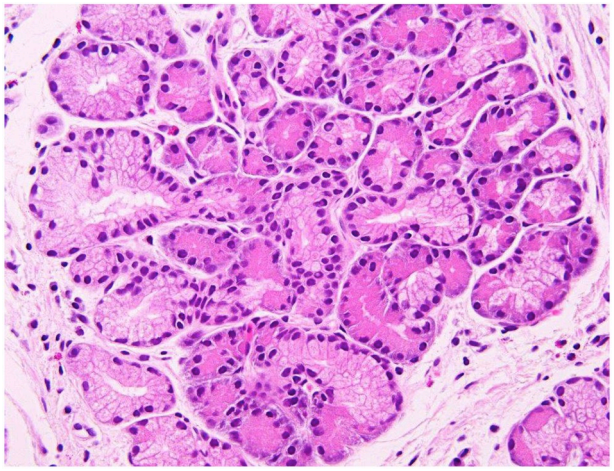

Fig. 6. Pancreatic heterotopia is commonly encountered in the esophagus. Note the brightly eosinophilic granules in the acinar cells.

8. FAQ: which histologic patterns can mimic Barrett's esophagus?

Answer:

Both pancreatic acinar cell heterotopia and some gastric foveolar cells can show morphologic features that suggest intestinal metaplasia (Figs. 6-8). Pancreatic heterotopia contains cells with granules that are readily separated from goblet cells but some gastric foveolar cells take on a bluish hue or show weak alcianophilia on the Alcian blue stain if it is performed. It is also important to recall that intestinal metaplasia can be found in cardiac and cardio-oxyntic mucosa as a result of conditions that affect the stomach, such as *H. pylori*-associated gastritis and autoimmune gastritis. This is particularly important to remember when only GEJ biopsies are available for evaluation without any concurrent esophageal or gastric biopsies.

Inlet patches can also be mistaken for columnar lined esophagus. If the endoscopist has only provided a location in centimeters, the sample might be labeled “esophagus 15 cm”. Histologically most inlet patches consist of oxyntic type mucosa (containing parietal cells), but a transitional or cardiac pattern (lacking oxyntic glands) may also be found. Intestinal metaplasia in inlet patches is rare, found in about 1% of cases.

Multilayered epithelium can also be mistaken for Barrett's esophagus. It is a type of epithelium that has been associated with gastroesophageal reflux and that has some properties of intestinal type epithelium and some properties of squamous epithelium [19–22]. Because of these features, some observers believe that it is a precursor to Barrett's esophagus (a precursor to a precursor) [23]. However, it can also be encountered at the GE junction in the setting of gastritis due to *H. pylori* or gastritis of the autoimmune type or even in fetal autopsies

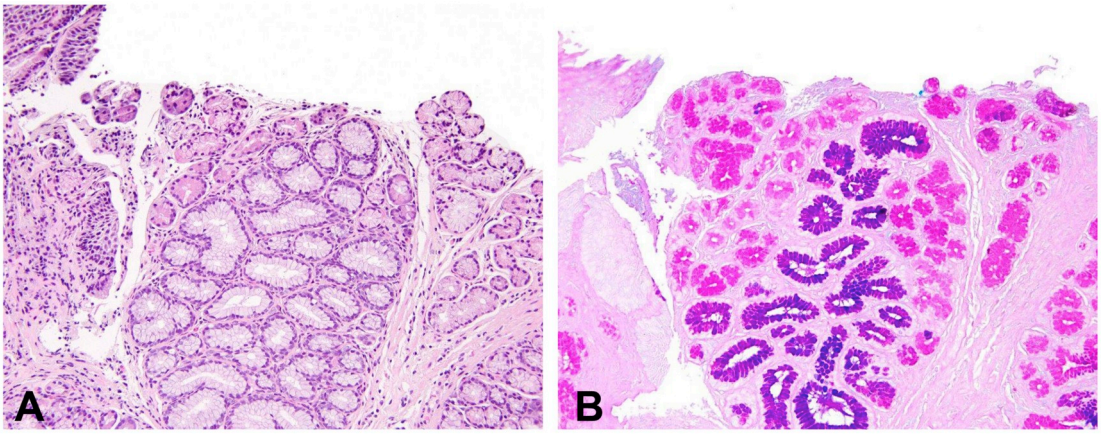

Fig. 7. Sometimes cardiac glands (A) display prominent alcianophilia (B) on PAS/Alcian blue staining. The bluish cells lack the morphologic features of goblet cells and such staining should not be interpreted as confirmation of intestinal metaplasia. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

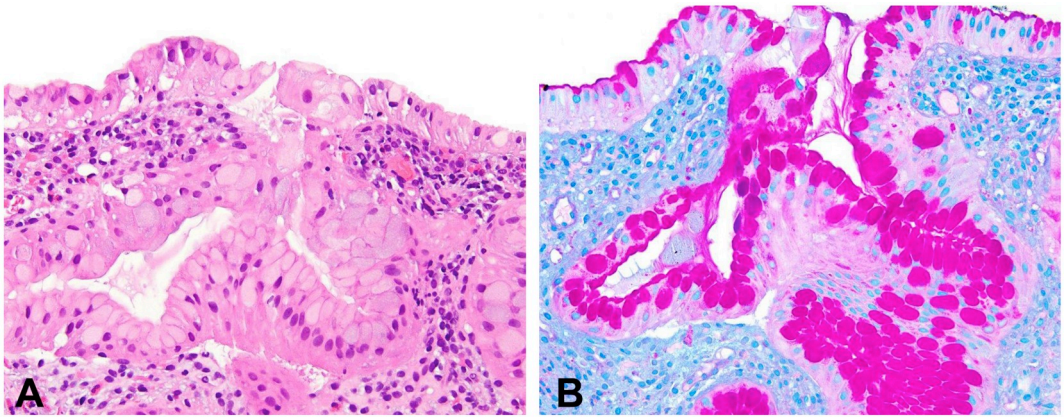

Fig. 8. The gastric foveolar cells in this case are distended with mucin (A) but they are not goblet cells. In this example, the same cells lack Alcian blue staining (B, PAS/Alcian blue stain). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

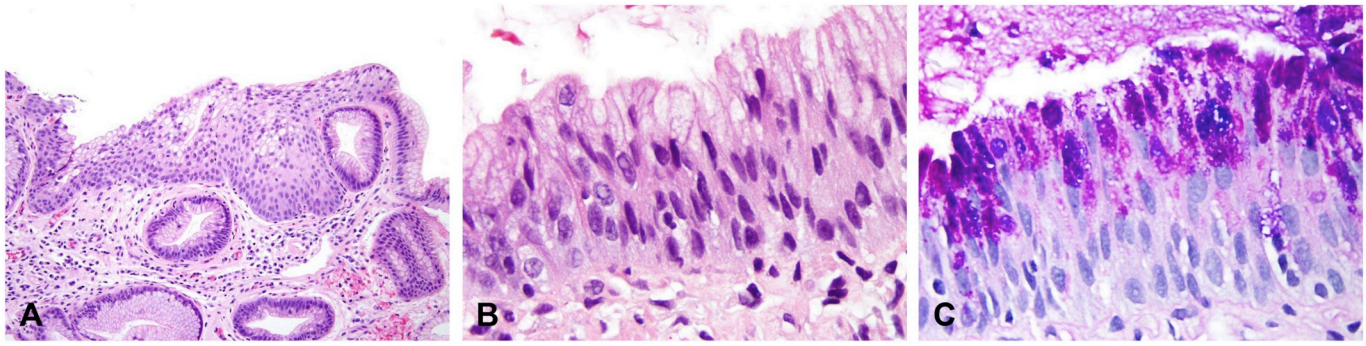

Fig. 9. Multilayered epithelium consists of a deeper zone of squamous cells and surface cells with columnar features (A). This image also shows cardiac type glands underneath squamous epithelium. Barrett's esophagus (with goblet cells) can also be found beneath squamous epithelium. At high magnification (B) of another example, the appearance is reminiscent of that of immature squamous metaplasia of the uterine cervix. Note the mucin droplets in some of the surface epithelial cells. PAS/Alcian blue staining of multilayered epithelium (C) shows a bluish hue that is not equivalent to intestinal metaplasia. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

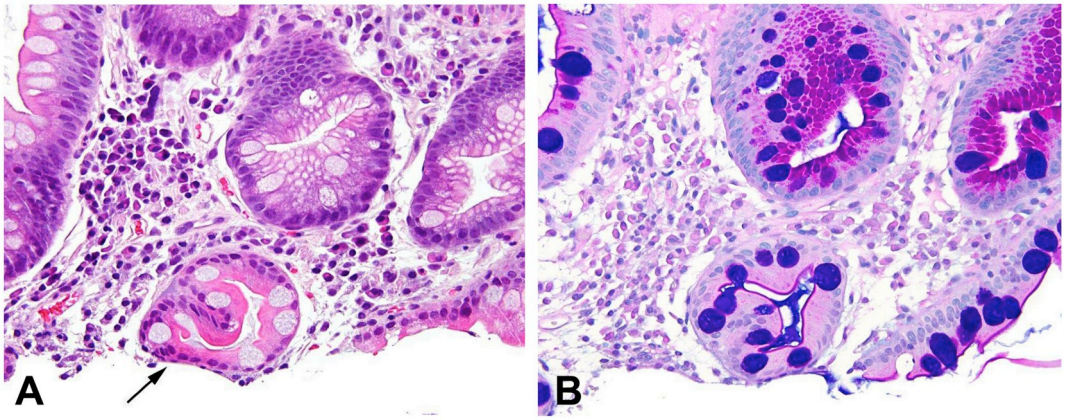

Fig. 10. Barrett's esophagus showing both complete and incomplete intestinal metaplasia. A. The gland in the lower part of the image (indicated) with complete intestinal metaplasia contains both goblet cells and absorptive cells in a fashion that *completely* mimics intestine whereas the gland above with incomplete intestinal metaplasia contains goblet cells admixed with cells with gastric foveolar type mucin. B. A PAS/Alcian blue stain highlights the brush border and goblet cells in the gland with complete intestinal metaplasia and the magenta colored neutral mucin in the gland with incomplete intestinal metaplasia. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and it may simply be a type of transitional epithelium that characterizes the GE junction. Finding multilayered epithelium is, however, a clue that a sample has come from the GEJ or esophagus rather than the stomach.

Multilayered epithelium has an appearance similar to that of immature squamous metaplasia in the uterine cervix (Fig. 9). The surface has a few cells that have a blush of mucin and the base has a squamous appearance. The mucin can have a basophilic appearance akin to that of goblet cells but the mucin is not a single crisply delineated vacuole like that in goblet cells.

It is not necessary to report this type of epithelium but finding it merits a careful search for intestinal metaplasia.

9. FAQ: what is the difference between complete and incomplete intestinal metaplasia and do they matter?

Answer: Complete intestinal metaplasia indicates that the metaplasia perfectly recapitulates intestine in that there are goblet cells separated by absorptive cells that have a brush border but not any cytoplasmic mucin. Incomplete intestinal metaplasia has only "incompletely" converted from gastric cardiac mucosa to intestinal-type mucosa (Fig. 10). As such, there are goblet cells separated by cells that resemble gastric foveolar cells. The complete type is far more likely to be found in gastric mucosa than in intestinal metaplasia of the esophagus and its presence can suggest that the sample is from the stomach rather than the esophagus. However, complete intestinal metaplasia is not specific for gastric intestinal metaplasia. The incomplete type, epidemiologically, is more likely to progress to adenocarcinoma than the complete type but reporting it is not particularly relevant in any given patient and it is not necessary to report which type is seen unless the purpose is a study protocol.

10. FAQ: are special stains needed to diagnose Barrett's esophagus?

Answer: Special stains are not needed [24,25].

11. Conclusion

In summary, reporting samples containing columnar epithelium from the GEJ and tubular esophagus provides important information that determines follow-up (or lack thereof). The key issues are 1) avoiding an interpretation of Barrett's esophagus when insufficient information is available to do so and 2) reporting which types of epithelium are seen.

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