Barrett Esophagus

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Frequently Asked Questions

1. What is the normal anatomy and histology of distal esophagus, gastroesophageal junction (GEJ), Z-line, and cardia?

- The esophagus is lined by stratified squamous epithelium and contains scattered submucosal salivary gland-like mucous glands.
- Endoscopically/grossly, the stomach begins at the most proximal aspect of the gastric folds. The gastric cardia is an extremely short segment of proximal stomach that is typically composed of surface foveolar columnar epithelium and either pure mucous or a mixture of mucous and oxyntic glands. The gastroesophageal junction (GEJ) is defined as the point where the distal esophagus meets the proximal stomach (cardia).
- Normally, the anatomic GEJ should correspond to the histologic transition point between the esophageal squamous epithelium and the gastric columnar epithelium, the so-called "Z-line" or squamocolumnar junctional (SCJ) mucosa. In response to injury from physiologic or pathologic gastroesophageal reflux disease (GERD), metaplastic columnar epithelium

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H. L. Wang, Z. E. Chen (eds.), *Practical Gastrointestinal Pathology*, Practical Anatomic Pathology,
https://doi.org/10.1007/978-3-030-51268-2_3

develops which extends proximally above the level of anatomic GEJ into the distal esophagus. Therefore, many adults have a proximally displaced or irregular Z-line with the SCJ located above the anatomic GEJ.

Reference: [1]

2. What is Barrett esophagus (BE)?

- Barrett esophagus (BE) is a condition that develops secondary to chronic injury from GERD. In patients with BE, metaplastic columnar epithelium that predisposes to the development of esophageal cancer replaces the stratified squamous epithelium that normally lines the distal esophagus.

Reference: [2]

3. What are the endoscopic findings in BE?

- Endoscopically, the GEJ is identified as the most proximal extent of the gastric folds. BE is recognized as salmon-colored columnar mucosa that extends in tongue-shaped projections above the GEJ and into the grayish squamous mucosa of the distal esophagus.

References: [3, 4]

4. What are the diagnostic criteria for BE and how does it differ worldwide?

- The diagnosis of BE requires endoscopic evidence that columnar mucosa extends above the GEJ into the distal esophagus, in addition to esophageal biopsy results that confirm the presence of columnar metaplasia. However, the criteria used to diagnose BE vary worldwide, and the main difference is in regard to the histologic type of columnar mucosa that establishes a diagnosis of BE. The metaplastic columnar epithelium may consist of a variety of cell types, including gastric-type non-goblet mucinous cells as well as intestinal-type goblet cells with variable enterocytes, Paneth cells, and endocrine cells (Fig. 3.1).
- In the United States and part of Europe, the presence of intestinal metaplasia (IM) with goblet cells within metaplastic columnar mucosa is required for diagnosis of BE, whereas in the United Kingdom and Japan, only the presence of columnar mucosa is required, and there is no need for the presence of IM (i.e., goblet cells). This difference is attributed to the difference in cancer risk between these two types of mucosal changes. Currently in the United States, intestinal-type epithelium with goblet cells is the only type of metaplastic columnar epithelium that is clearly shown to be associated with significant cancer risk and hence the current requirement for histologic confirmation of the presence of goblet cells.
- According to the 2016 criteria of American College of Gastroenterology (ACG), "BE should be diagnosed when there is extension of salmon-colored mucosa into the tubular esophagus extending ≥1cm proximal to the GEJ with biopsy confirmation of intestinal metaplasia."

References: [4–7]

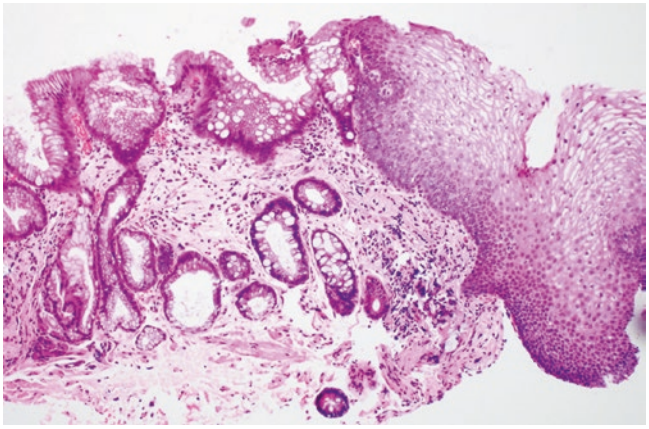

Fig. 3.1 Barrett esophagus. BE represents metaplastic conversion of normal squamous epithelium of the distal esophagus to columnar epithelium composed of those normally seen in the stomach (i.e., mucinous cells) as well as intestine (i.e., goblet cells and less frequently enterocytes, endocrine cells, and Paneth cells). The crypts show slight architectural irregularity and budding. The lamina propria shows a minimal lymphoplasmacytic infiltrate

5. Is there a required length of columnar mucosa for a diagnosis of BE?

- Yes, the recent definition of BE (2016 ACG) adds a required length of columnar/intestinal-type mucosa (≥1 cm proximal to the GEJ) which was not present in previous definitions. The reason for this change is due to very low risk of esophageal adenocarcinoma in patients that have IM limited to the GEJ as well as high interobserver variability among gastroenterologists in detecting the GEJ.

Reference: [4]

6. What are pseudo-goblet cells and how are they distinguished from true goblets cells?

- Presence of true goblet cells is required for a diagnosis of IM and therefore BE in the United States. Pseudo-goblet cells are foveolar epithelial cells that have distended cytoplasm due to abundant cytoplasmic mucin and can be mistaken for true goblet cells. Pseudo-goblet cells are typically found in clusters and linear rows at the superficial part of the epithelium, whereas true goblet cells are more sparsely distributed among intervening non-goblet columnar cells. True goblet cells have a distinctive cytoplasmic vacuole that compresses the nucleus and contain acid mucin which imparts a blue hue to the mucin vacuole on H&E stain (Fig. 3.2a, b).

Reference: [8]

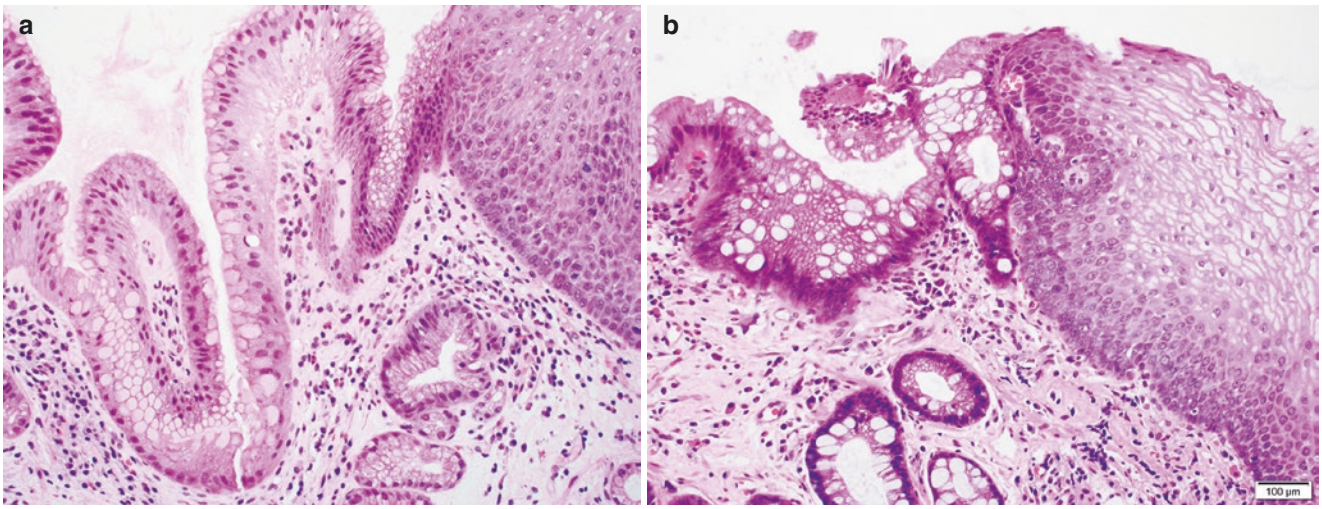

Fig. 3.2 True vs pseudo-goblet cells. In the United States, identification of goblet cells in the metaplastic columnar epithelium is required for the diagnosis of BE. Pseudo-goblet cells (**a**) may be mistaken for true goblet cells (**b**). In contrast to true goblet cells, pseudo-goblet cells are often arranged in clusters and linear rows and show distended cytoplasm without the characteristic triangle-shaped nucleus of true goblet cells

7. What is the best way to distinguish true versus pseudo-goblet cells, and are special stains such as periodic-acid-Schiff (PAS) and/or Alcian blue helpful in this distinction?

- The best way to distinguish true from pseudo-goblet cells is morphology on routine H&E-stained slides. There are no histochemical stains that can reliably distinguish the two and can be used on esophageal biopsies to help diagnose BE. While the acid mucin of true goblet cells stain blue with Alcian blue stain at pH of 2.5, pseudo-goblet cells usually reveal weak positivity as well. Overall, there is insufficient evidence to justify routine use of ancillary histochemical or immunohistochemical studies such as Alcian blue and/or PAS stains to identify goblet cells.

Reference: [25]

8. Are immunostains indicated to aid in diagnosis of BE?

- Based on the current evidence, the use of intestine-specific mucin glycoprotein immunostains or markers of intestinal differentiation (CDX2, Das-1, villin, Hepar 1, or SOX 9) is not indicated to aid in the diagnosis of BE.

Reference: [25]

9. What is the goal of screening and surveillance in patients with BE?

- BE is a known precursor and risk factor for the development of esophageal adenocarcinoma (EAC) which evolves through a metaplasia-dysplasia-carcinoma sequence. The goal of endoscopic surveillance in patients with BE is the early detection of neoplasia. At present, the morphologic identification and grade of dysplasia in endoscopic mucosal biopsies is the standard method of detecting patients at increased risk of developing EAC. Systematic four-quadrant surveillance biopsies taken at 1–2 cm intervals are recommended in patients with BE to detect early, treatable neoplasia.

Reference: [6]

10. How should GEJ biopsies be evaluated, and should patients with IM of GEJ undergo endoscopic surveillance?

- Obtaining biopsy of an irregular GEJ or Z-line is not recommended, if this is the only endoscopic abnormality. However, pathologists continue to receive GEJ biopsies for evaluation to "rule out BE," in patients who have been found to have an "irregular" endoscopic Z-line. Up to 30% of patients develop IM in the GEJ, which can happen secondary to injury from GERD and/or H. pylori infection. In patients who have an irregular Z-line and in whom biopsy samples of the GEJ have been obtained, additional biopsy sampling of mucosa above Z-line and from distal stomach may help interpretation of the etiology of the injury. However, regardless of the presence or absence of IM, these patients are not at significantly increased risk of malignancy, and current guidelines do not recommend surveillance of patients with IM in the GEJ only.

Reference: [9]

11. What is the significance of basal crypt atypia in BE?

- BE commonly shows atypia of basal crypt epithelium and this should not be misinterpreted as dysplasia. Crypts may show mild crowding at the base with mild pseudostratification of nuclei, hyperchromasia, typical mitotic figures, and mild nuclear enlargement with nuclei that are 1–2 times the size of a lamina

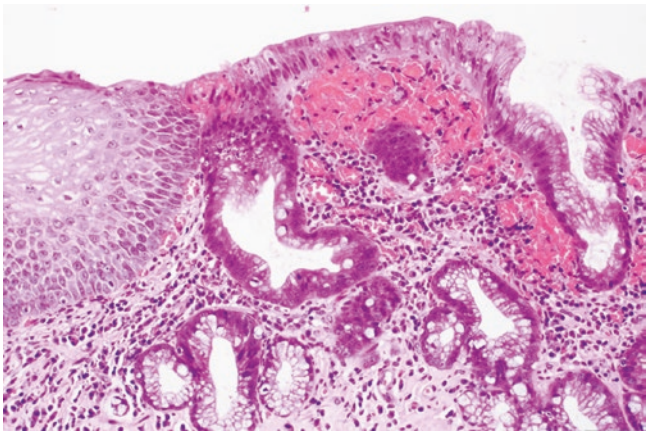

Fig. 3.3 Basal crypt atypia, non-dysplastic (case 1). Basal crypt epithelium is mildly hyperchromatic with enlarged nuclei, nuclear crowding, and pseudostratification. The epithelium matures toward the surface with basally located nuclei and abundant cytoplasm

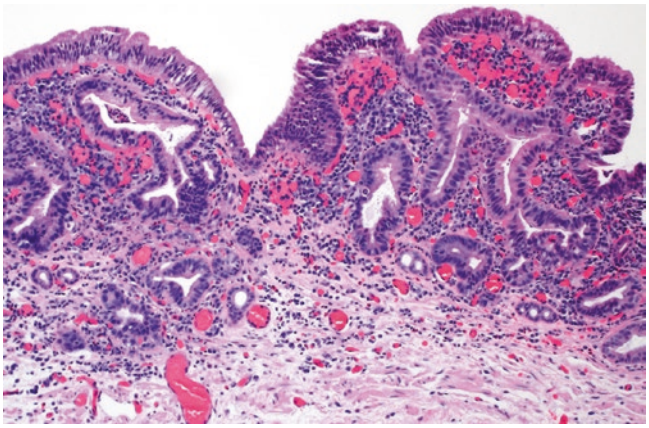

Fig. 3.4 Barrett esophagus, indefinite for dysplasia. In this biopsy, there is atypia of the epithelium with crowded, elongated nuclei that extend to the mucosal surface. The epithelium contains many intraepithelial neutrophils that raise the possibility of reactive epithelial changes. Goblet cells were present in other adjacent areas

propria fibroblast or endothelial cells (Fig. 3.3). However, this atypia is mild and limited to crypt epithelium, and normal "maturation" is seen toward the luminal surface. This maturation is characterized by progressive accumulation of abundant mucinous cytoplasm, with nuclei that are basally located and maintain polarity with respect to the basement membrane and a low nuclear-to-cytoplasmic ratio. The lamina propria is abundant without glandular architectural crowding or complexity.

- In some cases, the atypia of crypt epithelium is more than typically seen in metaplastic epithelium. In these cases, additional levels may be performed to ensure that there is no full-thickness atypia to the epithelium, which would then be considered true dysplasia.

References: [10, 12, 13]

12. In what situations should you diagnose BE with epithelial alterations indefinite for dysplasia?

- In several situations, Barrett epithelium may show cytologic or architectural abnormalities that raise the possibility of neoplasia/dysplasia, but it is difficult to be certain. In these settings, a diagnosis of indefinite for dysplasia is considered appropriate. For example, cytologic abnormalities may be present in the setting of active inflammation or ulceration. These regenerative and inflammatory changes may alter the maturation of the epithelium toward the surface, with cytologic changes including mucin depletion, nuclear hyperchromasia and crowding, and increased mitotic figures. In this setting, a diagnosis of "indefinite for dysplasia" confers uncertainty as to whether the epithelial changes are reactive or neoplastic in nature (Fig. 3.4). Generally, a rebiopsy is performed after the resolution of active inflammation.
- A diagnosis of indefinite for dysplasia may also be used in several other situations when technical difficulties in interpretation of the biopsy are present. Situations in which this may be appropriate include:
  - Tangential sectioning.
  - Poorly oriented tissue fragments.
  - Thick sections, poor staining or fixation, cautery artifact.
  - Significant basal crypt atypia when the surface is not present for evaluation or assessment of maturation is not possible.
- If a diagnosis of "indefinite for dysplasia" is rendered, it is helpful to comment in the pathology report the underlying reason for the indefinite diagnosis as medical therapy may be maximized in cases of ongoing reflux effect/inflammation, and diagnostic yield in subsequent rebiopsy may be optimized.

References: [10, 12]

13. How do you determine reactive atypia versus dysplasia in BE?

- In the presence of active inflammation or ulceration, nonneoplastic epithelium can demonstrate hyperchromasia, mucin loss, and nuclear crowding that can mimic dysplasia.
- A gradual, non-abrupt transition from non-atypical to atypical mucosa favors reactive epithelial changes. A lack of glandular architectural abnormalities such as crowded, cribriform glands also favors reactive changes.
- Reactive cardia-type mucosa demonstrates a "top heavy" distribution of atypia with surface nuclear stratification and bland-appearing cytology in the deeper mucosa.

References: [10, 12, 14]

14. What are the histologic features of low-grade dysplasia in BE?

- Low-grade dysplasia is noninvasive neoplastic epithelium most often resembling intestinal-type dysplasia as seen in adenomas of the colon.
- The epithelium shows full-thickness atypia extending from crypts to surface epithelium. Cytologic features include elongated and crowded nuclei with pseudostratification and hyperchromasia, typically limited to the basal aspect of the cytoplasm (Fig. 3.5). Nuclei generally remain polarized with orientation of the long axis of the nuclei perpendicular to the basement membrane. In general, there is an abrupt transition from non-dysplastic to dysplastic epithelium.
- Goblet cells are typically present but may be depleted.
- The glandular architecture is typically not crowded.
- The histologic features of low-grade dysplasia and non-dysplastic BE mucosa are also summarized in Table 3.1.

References: [10, 12, 16–18]

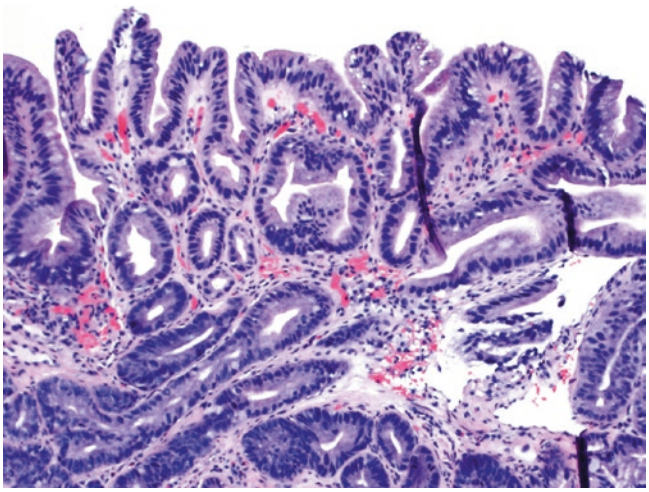

Fig. 3.5 Barrett esophagus with low-grade dysplasia. The epithelium shows full-thickness atypia without surface maturation. The nuclei are enlarged and hyperchromatic but maintain polarity to the basement membrane and retain some apical cytoplasm. There is no significant glandular crowding or complexity

15. What are the histologic features of high-grade dysplasia in BE?

- High-grade dysplasia is noninvasive neoplastic epithelium with high-grade cytologic and/or architectural abnormalities.
- The cytologic atypia is more severe than in low-grade dysplasia, with more pronounced nuclear enlargement, increased nuclear-to-cytoplasmic ratios, loss of nuclear polarity with respect to the basement membrane, and prominent nucleoli (Fig. 3.6).
- Mitotic figures may be seen in the surface epithelium.
- Architectural changes in the epithelium are also present in high-grade dysplasia including villiform morphology, glandular crowding and cribriform glands, intraluminal budding, and branching and lateral budding of crypts.
- Focal glandular intraluminal necrosis may also be present.
- Goblet cells may be depleted.

References: [10–12, 19]

Table 3.1 Histologic features of Barrett mucosa and its progression to intramucosal adenocarcinoma

Barrett esophagus	Non-dysplastic	Low-grade dysplasia	High-grade dysplasia	Intramucosal adenocarcinoma
Cytology	Mild nuclear enlargement and hyperchromasia Scattered crypt mitotic figures	Nuclear enlargement, elongation extending from crypt base to surface Nuclear stratification limited to basal half of cell cytoplasm Increased N/C ratio Preserved or only mild loss of nuclear polarity Increased mitoses, usually limited to crypts	Nuclear enlargement Full-thickness nuclear stratification Mild to marked nuclear pleomorphism Irregular nuclear contours Vesicular chromatin Prominent loss of nuclear polarity Mitoses on surface epithelium Increased number of atypical mitoses	Similar to high-grade dysplasia
Architecture	Preserved	Relatively preserved	Cribriform and crowded glands Irregulary sized and shaped crypts with crypt branching Intraluminal budding Intraluminal necrosis	Single cells in lamina propria Sheets of neoplastic cells Anastomosing pattern of glands Angulated infiltrative glands Intraluminal necrosis

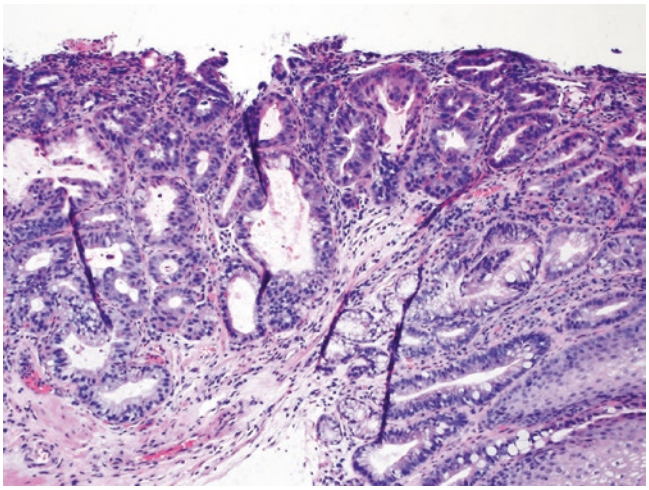

Fig. 3.6 Barrett esophagus with high-grade dysplasia. The epithelium shows full-thickness atypia, with enlarged, round, crowded nuclei with a loss of polarity. There are complex cribriform glandular architecture and glandular crowding. Focal glandular luminal necrosis is present

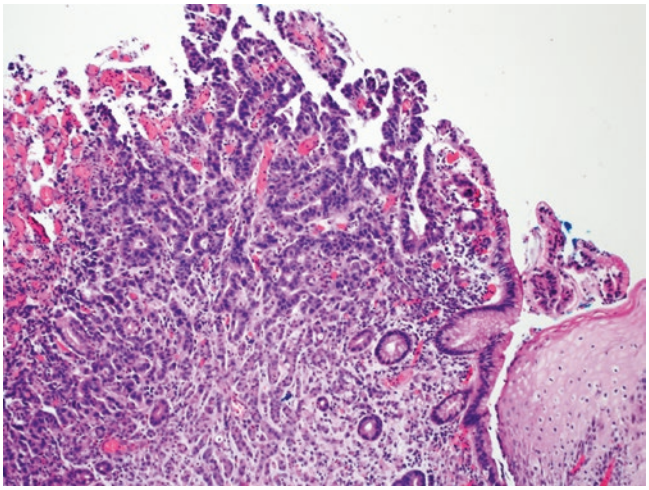

Fig. 3.7 Barrett esophagus with intramucosal adenocarcinoma. The epithelial cells show a never-ending anastomosing glandular pattern and single neoplastic cells within the lamina propria

16. How do you distinguish high-grade dysplasia from intramucosal adenocarcinoma in BE?

- Intramucosal adenocarcinoma describes architectural changes in which neoplastic epithelium has invaded beyond the basement membrane into the lamina propria or muscularis mucosae, but has not penetrated the deep layer of the muscularis mucosa into the submucosa.
- Single-cell invasion into lamina propria (cells that do not have connection to glands), sheets of malignant cells, angulated and infiltrative glands, and a complex "never-ending" anastomosing glandular pattern are architectural features that indicate intramucosal adenocarcinoma (Fig. 3.7).
- Intraluminal necrosis within neoplastic glands and prominent nucleoli are often seen in intramucosal adenocarcinoma.
- The histologic distinction between high-grade dysplasia and intramucosal adenocarcinoma is outlined in Table 3.1.

References: [10, 12, 15, 17, 21]

17. How do you identify submucosally invasive adenocarcinoma?

- Endoscopic biopsy specimens from patients with BE are typically superficial, with sampling of epithelium and lamina propria.
- Most patients with BE have areas of duplicated muscularis mucosae that can lead to the appearance of neoplastic glands invading through the muscularis mucosae, while the glands are actually still within the lamina propria (Fig. 3.8).
- Owing to the superficial nature of biopsies, it is difficult to accurately diagnose submucosally invasive adenocarcinoma in a biopsy specimen. When neoplastic epithelium is present within desmoplastic stroma, this is convincing evidence of submucosal invasion.
- In endoscopic mucosal resection or endoscopic submucosal dissection specimens, the deepest layer of muscularis mucosae may be present, and submucosa

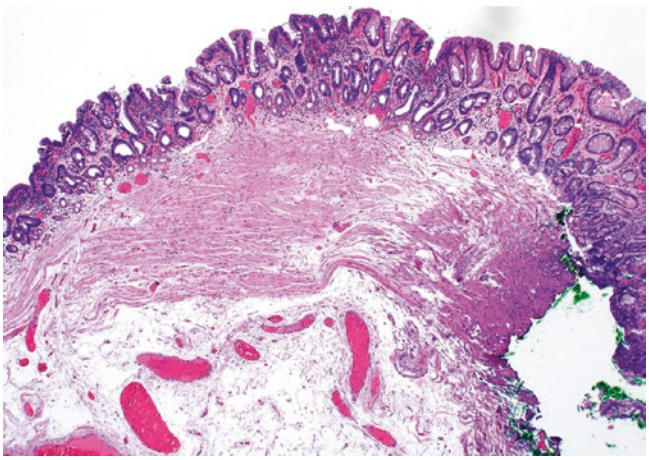

Fig. 3.8 Barrett esophagus with a duplicated muscularis mucosae. This endoscopic mucosal resection specimen shows BE with a thickened and duplicated muscularis mucosae. This muscle layer can be mistaken for muscularis propria, which may lead to overstaging of BE neoplasia

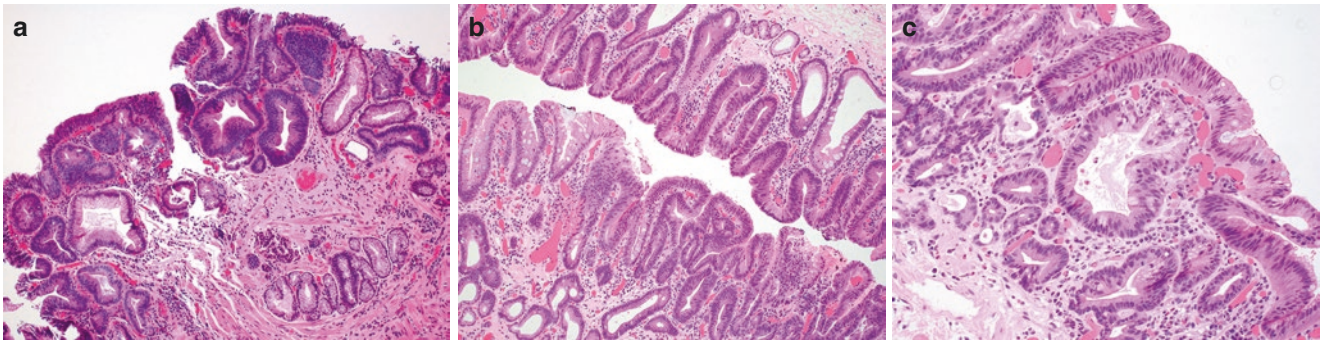

Fig. 3.9 Types of dysplasia seen in Barrett esophagus. (**a**) Intestinal type resembling a tubular adenoma of the colon. (**b**, **c**) Foveolar type featuring gastric foveolar-type cytoplasm with nuclear dysplastic changes. Note the transition from non-dysplastic BE mucosa (left) to dysplastic mucosa (right) in panel **b**. Panel **c** shows a progression from low-grade (right) to high-grade (left) dysplasia

is more readily identified. In well-oriented tissue profiles, submucosal invasion can be accurately diagnosed and margins assessed.

References: [19, 23, 24]

18. What are the described types of nonconventional dysplasia and how are they identified?

- The most common histologic appearance of dysplasia is intestinal type, which resembles the dysplasia seen in adenomas of the colon (Fig. 3.9a).
- Two additional histologic variants of dysplasia have been described including gastric foveolar dysplasia and serrated dysplasia.
- Gastric foveolar dysplasia (Fig. 3.9b, c) is characterized by mucinous epithelium with gastric foveolar-type cytoplasm and rare goblet cell differentiation. The cells may be cuboidal or low columnar in shape with a single layer of enlarged round nuclei with open chromatin, prominent nucleoli. The epithelium typically shows a crowded glandular architecture (back-to-back glands). Elongated and pseudostratified nuclei can be seen in cases of low-grade dysplasia (Fig. 3.9b, c). A sharp transition from non-dysplastic epithelium can be seen.
- Serrated dysplasia is characterized by architecture similar to serrated polyps of the colon, with a sawtooth pattern of crypt epithelium when cut longitudinally, or a star-shaped lumen on cross section. The nuclei in serrated dysplasia are oval with open chromatin, while the cytoplasm is typically more eosinophilic.
- Criteria for low- and high-grade dysplasia in gastric foveolar and serrated dysplasia are not well established, but in general, cytologic atypia and architectural complexity are used for the distinction.

References: [21, 22]

19. Is ancillary testing recommended in identifying dysplasia associated with BE or those at risk of progression?

- Morphologic assessment remains the gold standard for identifying dysplasia.
- Recent consensus guidelines from the gastrointestinal pathology society do not recommend ancillary testing at this point in time.
- Some studies have suggested that immunohistochemical staining for p53 is helpful in identifying dysplasia and those at risk of progression. Overall there are insufficient criteria for how to interpret this stain including lack of clarity in the implications of the staining patterns on the presence and grading of dysplasia, as well as the possibility of progression. The overall evidence is not sufficient to recommend this ancillary test for routine use at this point in time.
- Immunohistochemical stains for AMACR, cyclin D1, SOX2, Ki-67, and others have been investigated in the diagnosis of BE dysplasia, with some showing promise for identification of dysplasia or risk of progression. More recent studies have questioned the specificity of some of these markers, and further studies are needed to assess their utility in clinical practice.

Reference: [25]

20. What are the possible treatment modalities when a diagnosis of dysplastic BE is rendered?

- Flat low-grade dysplasia may be treated with surveillance or endoscopic ablation.
- Flat high-grade dysplasia and intramucosal adenocarcinoma are typically managed with endoscopic radiofrequency ablation.
- Nodular lesions are treated by endoscopic mucosal resection/endoscopic submucosal dissection. Follow-up may include additional radiofrequency ablation.

- If submucosal invasion or presence of unfavorable histology (poor differentiation or lymphovascular invasion) is identified, treatment is discussed with a multidisciplinary oncology group.

Reference: [4]

21. Is evaluation of BE dysplasia reproducible between pathologists?

- There is known interobserver variability among pathologists in the diagnosis of BE dysplasia, even among expert gastrointestinal pathologists. This variability is higher for indefinite and low-grade dysplasia.
- In patients with dysplasia of any grade, it is recommended that the biopsy be reviewed by two pathologists, one of which has expertise in gastrointestinal pathology.

References: [11, 20, 26, 27]

Case Presentation

Case 1

Learning Objectives

1. To understand the diagnostic criteria for BE
2. To understand the implication of evaluating GEJ biopsies

Case History

A 47-year-old male undergoes upper gastrointestinal endoscopy due to dyspepsia. Endoscopically, GEJ appears irregular, but there are no other abnormalities seen. Biopsies of irregular GEJ are obtained to "rule out BE".

Histologic Findings

Squamous epithelium is seen on the left. There is mucinous columnar epithelium on the right with mild chronic and focal active inflammation. Scattered goblet cells are also present among gastric-type columnar epithelia. The presence of goblet cells indicates IM (Fig. 3.3).

Final Diagnosis

Columnar mucosa with mild chronic active inflammation. IM is present.

Take-Home Messages

- BE is defined as the presence of IM in biopsies taken ≥1 cm above GEJ.
- Presence of IM in GEJ biopsies does not necessarily indicate BE. While theoretically, this could be an extension of more extensive BE, it is not clear based on this biopsy alone, and therefore the pathologists should only report the presence of IM but not designate this as BE.

Case 2

Learning Objectives

1. To understand the clinical and endoscopic presentation of patients with BE
2. To understand the pathologic features of BE with dysplastic epithelium

Case History

A 67-year-old Caucasian male with a long history of reflux symptoms is referred to gastroenterologist by his primary care physician.

Endoscopic Findings

An upper endoscopy shows tongues of salmon-colored mucosa extending 4 cm upward from GEJ into the distal esophagus. Biopsies were obtained in four quadrants every 1–2 cm with jumbo forceps.

Histologic Findings

- Histologic sections demonstrate columnar mucosa with IM (Fig. 3.10a).
- Basal crypt atypia is present, which is expected in BE.
- In some areas, there is an abrupt transition from maturing epithelium to full-thickness cytologic atypia (Fig. 3.10b).
- The nuclei are enlarged and hyperchromatic, with crowding and pseudostratification.
- The long axis of the nuclei remains perpendicular to the basement membrane, and they are located in the basal half of the cytoplasm.
- There is no glandular architectural crowding or complexity.

Differential Diagnosis

- Barrett esophagus
- Barrett esophagus with low-grade dysplasia
- Barrett esophagus with high-grade dysplasia

IHC and Other Ancillary Studies

None.

Final Diagnosis

Barrett esophagus with low-grade dysplasia.

Take-Home Messages

- BE with low-grade dysplasia is characterized by hyperchromatic nuclei that extend from the crypt base to the surface epithelium.
- The nuclei maintain polarity with respect to the basement membrane.
- The dysplastic epithelium shows no architectural complexity.

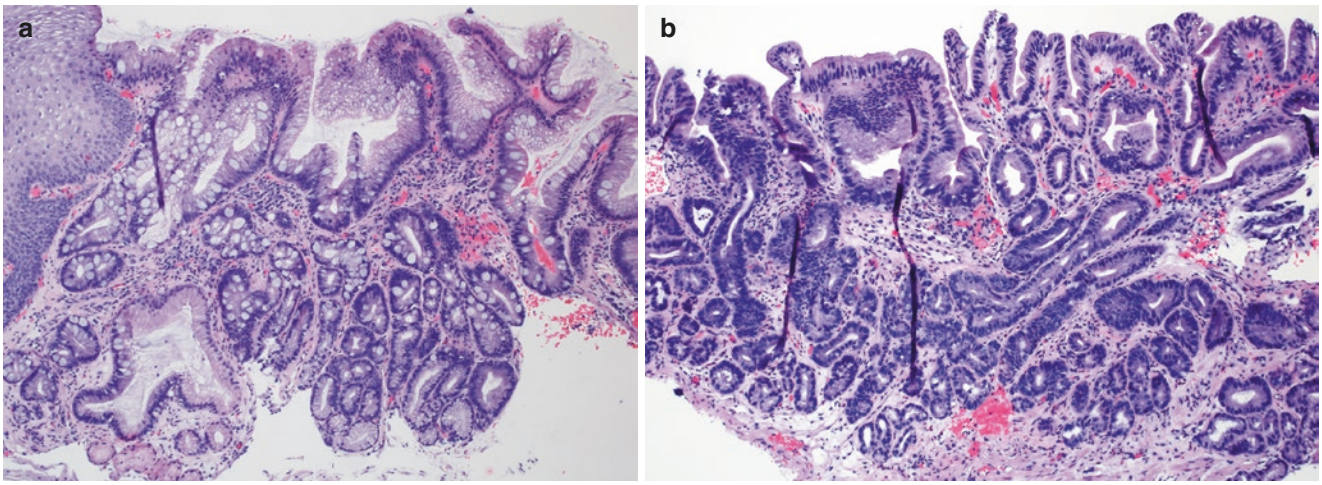

Fig. 3.10 Distal esophageal biopsy (case 2) showing IM (**a**) and areas of full-thickness cytologic atypia (**b**)

Case 3

Learning Objectives

1. To understand the clinical and endoscopic presentation of patients with BE
2. To understand the pathologic features of BE and dysplastic epithelium

Case History

A 73-year-old Caucasian male presented for follow-up for his known BE. His last endoscopic screening was 3 years prior and biopsies were negative for dysplasia.

Endoscopic Findings

On endoscopic examination, chromoendoscopy noted an irregular/distorted mucosal pattern in the distal esophagus with a small nodule identified. Endoscopic mucosal resection of the nodule was performed.

Histologic Findings

- Histologic sections demonstrate columnar mucosa with focal IM.
- The epithelium shows full-thickness atypia with hyperchromatic, enlarged round nuclei with prominent nucleoli, loss of nuclear polarity, and high nuclear-to-cytoplasmic ratios (Fig. 3.11a).
- The epithelium shows architectural complexity including crowded cribriform glands and a "never-ending" anastomosing glandular pattern (Fig. 3.11b).

Differential Diagnosis

- Barrett esophagus
- Barrett esophagus with low-grade dysplasia
- Barrett esophagus with high-grade dysplasia
- Barrett esophagus with intramucosal adenocarcinoma

IHC and Other Ancillary Studies

None.

Final Diagnosis

Barrett esophagus with intramucosal adenocarcinoma.

Take-Home Messages

- BE with intramucosal adenocarcinoma is characterized by high-grade cytology. Architectural features of intramucosal adenocarcinoma include single cells in the lamina propria or complex, never-ending anastomosed glands.

Case 4

Learning Objectives

1. To understand the diagnostic criteria for IM
2. To understand the difference between true and pseudo-goblet cells

Case History

A 58-year-old male presented with reflux symptoms.

Endoscopic Findings

An upper endoscopy revealed an irregular Z-line and a tongue of pink mucosa in the distal esophagus extending ~1.2 cm above the GEJ.

Histologic Findings

- Histologic sections demonstrate gastric-type columnar mucosa with a small island of multilayered cells.
- Some of the cells have intracytoplasmic mucin vacuoles with a blue hue (Fig. 3.12a).

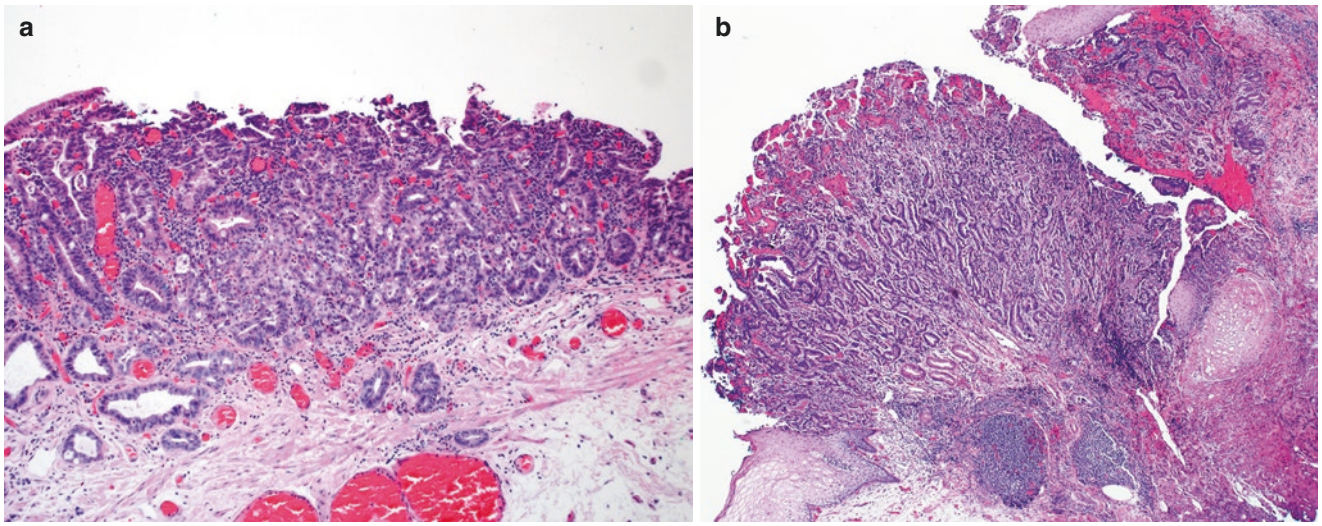

Fig. 3.11 Endoscopic mucosal resection of a small nodular lesion in the distal esophagus from a patient with long-standing history of Barrett esophagus (case 3). Sections show full-thickness epithelial atypia with enlarged round and hyperchromatic nuclei (**a**). There is glandular architectural complexity with a "never-ending" anastomosing pattern (**b**)

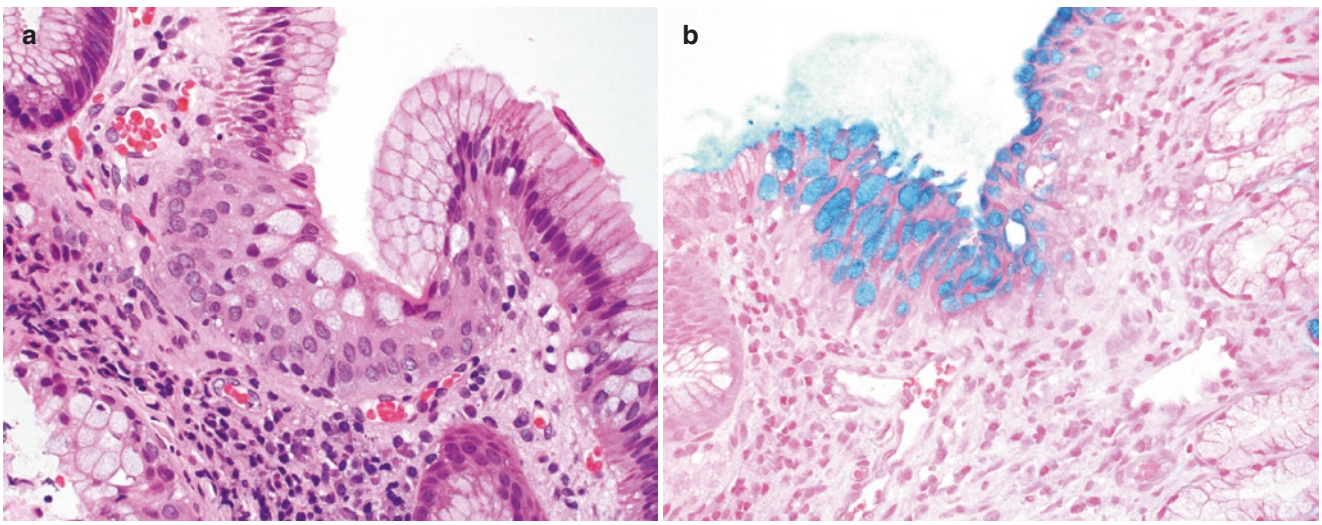

Fig. 3.12 Distal esophageal biopsy (case 4) showing clusters of mucin-containing cells (**a**) that stain blue on Alcian blue at pH 2.5 (**b**)

Differential Diagnosis

- Intestinal metaplasia, consistent with Barrett esophagus
- Pseudo-goblet cells, no support for Barrett esophagus

IHC and Other Ancillary Studies

- Alcian blue stain at pH 2.5 shows "blue mucin" (Fig. 3.12b).

Final Diagnosis

Pseudo-goblet cells, no support for Barrett esophagus.

Take-Home Messages

- Pseudo-goblet cells can have "blue mucin" and even a "goblet" shape.
- Pseudo-goblet cells are typically arranged in clusters or linear rows, whereas true goblet cells are more dispersed among intervening non-goblet columnar cells.
- Alcian blue stain at pH 2.5 stains both true and pseudo-goblet cells blue and is not recommended as a routine stain to help diagnosis.
- True goblet cells are required for BE diagnosis in the United States.

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