Non-Barrett Esophagitis

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Esophagitis can be a frustrating diagnostic challenge as the esophagus has a limited number of mechanisms to deal with injury and many causes of esophageal damage create overlapping histologic pictures. While a pathology report may not be able to always offer a specific diagnosis, it is important to both exclude specific treatable conditions and recognize different patterns of injury that can produce a more precise differential diagnosis that, along with clinical history, endoscopic findings, and medication history, can lead a clinician to the proper treatment plan.

Frequently Asked Questions

1. What are the clinicopathologic features seen in gastroesophageal reflux disease (GERD)?

The diagnosis of GERD is multifactorial and is made using a combination of clinical and pathologic findings. Symptoms for GERD are nonspecific but typically consist of burning chest pain that can be worse at night when patients are supine and after eating, chronic cough, difficulty swallowing, and disrupted sleep. GERD is the most commonly diagnosed disorder in the gastrointestinal tract in the United States, and meta-analysis estimates that the prevalence of GERD is between 15 and 20% in North America and Europe. Risk factors for the development of GERD include advancing age, male gender, obesity, smoking, pregnancy, hypothyroidism, scleroderma, poor diet, alcohol, and medications. Endoscopic findings range from normal or mild inflammation to ulceration and stricture. According to the American College of Gastroenterology (ACG) guidelines, a presumptive diagnosis of GERD can be made without biopsy in the setting of typical symptoms of heartburn and regurgitation, and empiric therapy with a proton pump inhibitor (PPI) is instituted. Risk factors for long-term complications of GERD including Barrett esophagus and adenocarcinoma include increased age, Caucasian race, and male sex.

H. L. Wang, Z. E. Chen (eds.), *Practical Gastrointestinal Pathology*, Practical Anatomic Pathology,
https://doi.org/10.1007/978-3-030-51268-2_2

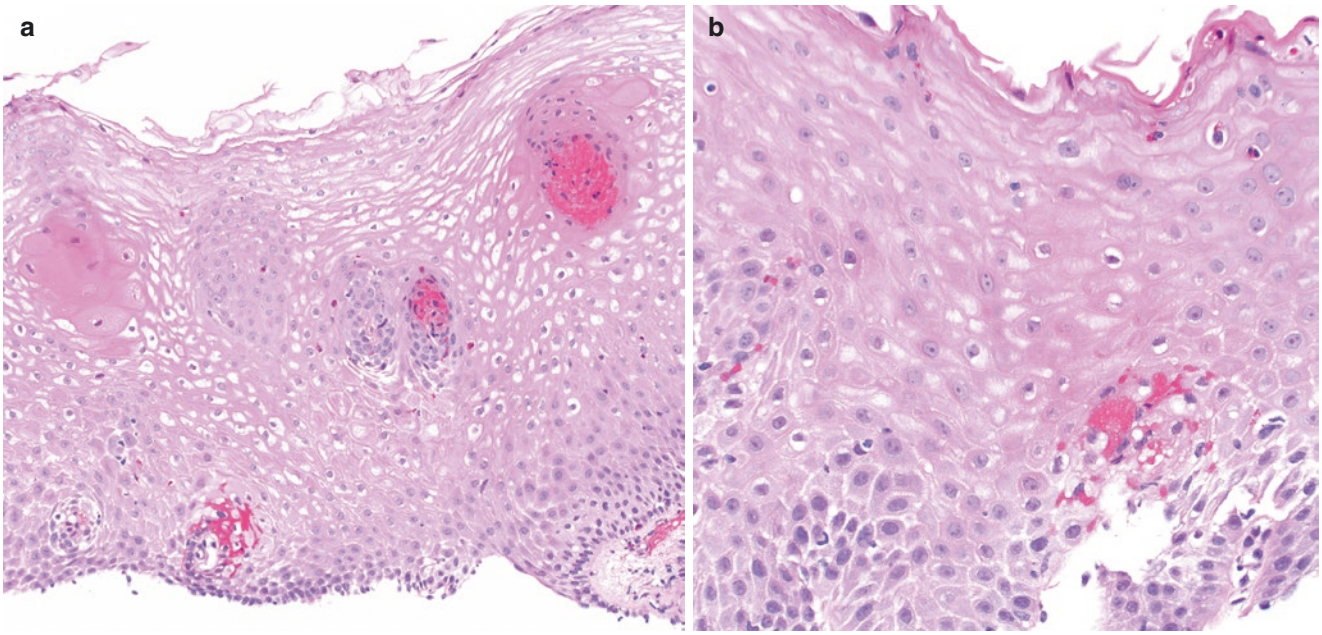

Fig. 2.1 Reflux esophagitis. (**a**) Scattered randomly distributed eosinophils, mild basal layer hyperplasia, elongated papillae, mild intercellular edema, and vascular lakes. (**b**) Additionally shows a superficial layer of parakeratosis

Biopsies of patients with GERD are frequently performed to exclude other types of esophagitis. The histologic features of biopsies in patients with GERD have been well described. These features include elongation of the papillae (>50% of the squamous epithelial thickness), hyperplasia of the basal layer (five to six layers or >15%), mildly increased intraepithelial eosinophils, and dilated intercellular spaces (Fig. 2.1a, b). Increased lymphocytes, keratinocyte vacuolization, vascular lakes, and balloon cells may also be seen. In contrast to eosinophilic esophagitis in which the eosinophils are typically more heavily concentrated near the epithelial surface, the eosinophils in GERD are randomly distributed within the epithelium. A mild parakeratosis at the luminal surface can also be seen. Although it is not practical to measure it in every esophageal biopsy, a recent study also found that increased epithelial thickness was a strong histologic marker for GERD. In the latter study, controls consisted of patients with upper gastrointestinal symptoms, but they did not need to have a different form of esophagitis so it is unclear how the epithelial thickness of GERD compares to that seen in other esophagitides such as eosinophilic or lymphocytic esophagitis. Neutrophils can be seen in more severe reflux esophagitis cases with erosions and ulceration. Unfortunately, these features are seen in other types of esophagitis which need to be excluded both clinically and histologically. Biopsies from the mid- and proximal esophagus can be helpful as these changes are usually concentrated in the distal esophagus in GERD as this is the area most heavily exposed to the refluxed gastroduodenal contents.

References: [1–10]

2. What are the clinicopathologic findings in eosinophilic esophagitis (EoE)?

The mechanism of disease in EoE is not fully understood, but it is currently defined as an immune- or antigen-mediated disease with esophageal dysfunction and eosinophil-predominant inflammation. EoE patients are more likely to have a history of allergic disease, and many EoE patients respond to dietary elimination of an offending food group. Seasonal variation in symptoms of EoE that mirrors that seen in allergic disease is further evidence of an association. EoE is relatively rare (1–5 per 10,000 persons in the United States and Europe), has a male gender predilection, and mostly has an onset between childhood and early to mid-adulthood. Symptoms of EoE typically include dysphagia and food impaction in adults and also include failure to thrive, heartburn, and difficulty eating in children. On endoscopy, EoE is classically described with esophageal furrowing or felinization (transverse folds in the esophagus) with possible vascular markings, rings, white exudates, and strictures, but these features are not entirely specific and biopsy is needed to confirm the diagnosis. In addition to biopsy, lack of response to PPI therapy (see question 4) and normal acid exposure on esophageal pH monitoring can aid in the diagnosis. Recent consensus recommendations first published in 2007 and updated in 2011 have aided in creating more uniformity in using both clinical and histologic criteria for making the diagnosis of EoE.

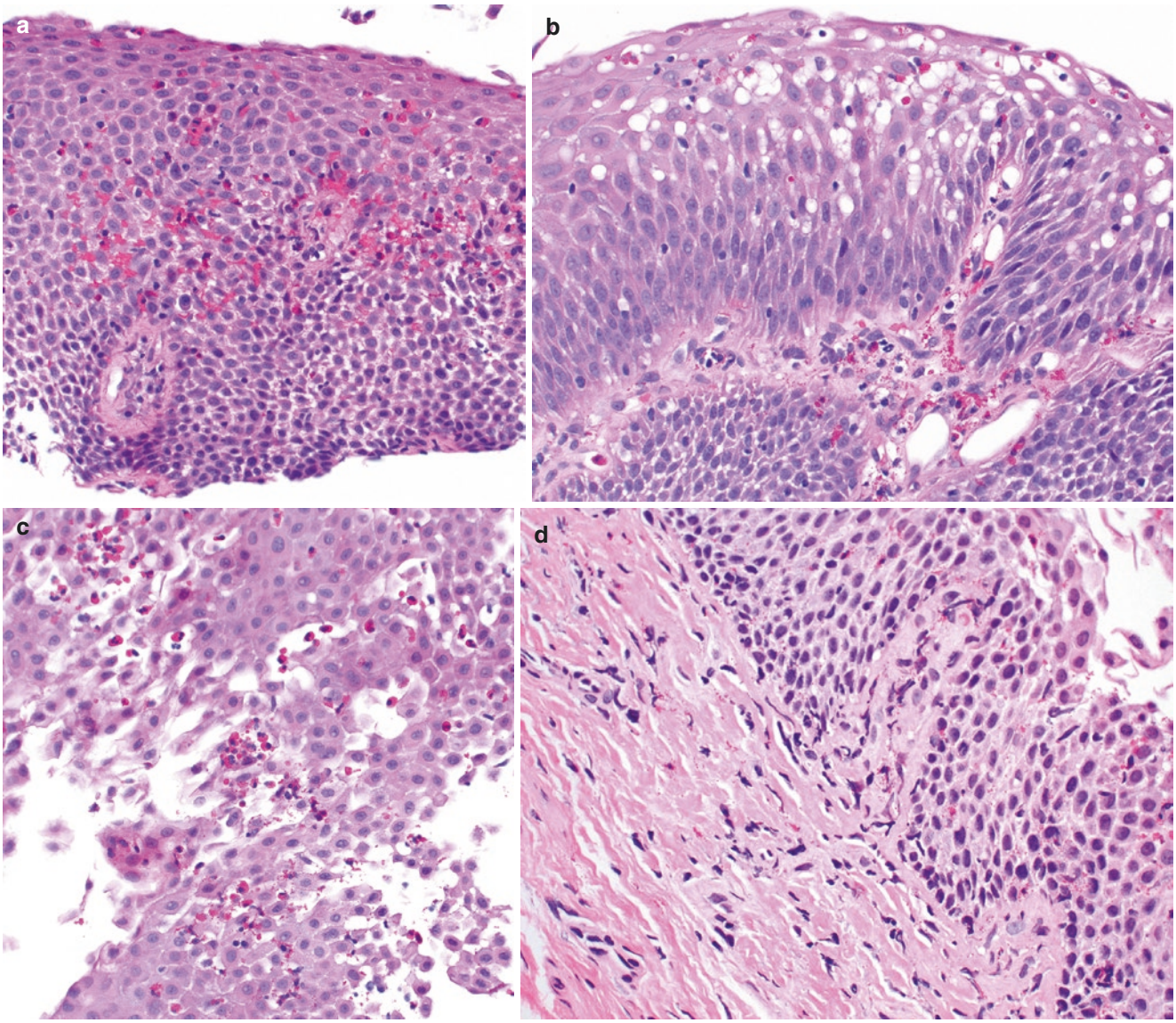

Fig. 2.2 Eosinophilic esophagitis. (**a**, **b**) Markedly increased intraepithelial eosinophils, marked basal layer hyperplasia, elongated papillae, and intercellular edema. (**c**) Degranulated eosinophils are also common and eosinophilic microabscesses can be present. (**d**) Lamina propria typically shows features of fibrosis

On histology, EoE is of course characterized by prominent eosinophils. The eosinophils are usually concentrated near the epithelial surface with degranulated eosinophils and eosinophilic microabscesses. At least 15 eosinophils in a high-power field are required for the diagnosis, but we will discuss eosinophil counts further in question 3. Biopsies also show marked reactive epithelial changes with a desquamated surface, pronounced basal cell hyperplasia, and elongation of the papillae (Fig. 2.2a–c). In contrast to GERD, eosinophil microabscesses and degranulation are common features, the basal cell hyperplasia is typically more pronounced (more than 50% of the epithelium compared to less than 25% in GERD), lamina propria fibrosis is more common, and histologic findings are typically present in the mid- and upper esophagus (Fig. 2.2d). Multiple biopsies from multiple locations within the esophagus are necessary as the histologic findings in EoE can be variable throughout the esophagus with biopsy fragments from a single location in the same patient showing both severe and mild to no disease. Biopsies from other sites in the gastrointestinal tract are important to exclude that the findings in the esophagus are isolated and not a portion of eosinophilic gastroenteritis. Recently, a composite histologic scoring system has been developed to aid in the diagnosis that is reported to outperform a simple eosinophil count. Table 2.1 compares the clinical and pathologic findings in GERD and EoE.

References: [11–18]

Table 2.1 Comparison of typical features of GERD and EoE

	GERD	EoE
Demographic		
Age	Older adults	Children and young adults
Sex	More common in males	More common in males
Main risk factor	Central adiposity	Allergic disease
Overlapping histologic factors	Intraepithelial eosinophils	Intraepithelial eosinophils
	Elongation of papillae	Elongation of papillae
	Basal layer hyperplasia	Basal layer hyperplasia
	Intercellular edema	Intercellular edema
	Parakeratosis	Parakeratosis
Distinguishing histologic features	Findings most pronounced in the distal esophagus	Findings in the mid- and upper esophagus with variation in findings across and within biopsies
	<15 eosinophils in a high-power field	>15 eosinophils in a high-power field
	No eosinophilic microabscesses	Eosinophilic microabscesses often seen
	Evenly distributed eosinophils throughout the epithelium	Eosinophils concentrated in the upper portion of the epithelium

3. How can counting intraepithelial eosinophils add valuable information to a pathology report?

The most common setting for which an eosinophil count is helpful is aiding in the differential diagnosis between reflux esophagitis and EoE. This can be a difficult distinction as both diseases feature reactive epithelial changes, basal zone hyperplasia, and elongated papillae. Eosinophil count is usually the most reliable manner to distinguish these two entities on histology. It should be noted that most reported eosinophil counts are based on a peak count in the most concentrated high-power field and that the threshold of 15 eosinophils to diagnose EoE is not based on established sensitivity and specificity testing, but is instead the lowest number of eosinophils seen in cases of eosinophilic esophagitis. One study from colleagues in Germany comparing the histologic features of these entities found that there was a mean of 55 (95% confidence interval (CI) 44–66) eosinophils in a high-power field compared to 9 (95% CI 5–13) in GERD. Cases with eosinophil counts in the middle of these ranges (10–20 eosinophils in a high-power field) can be a diagnostic challenge as they could represent severe GERD or mild EoE. Indeed the above referenced study found that 17% (4/24) of GERD cases had eosinophil counts of at least 15 in a high-power field. In these scenarios, it is difficult to provide a definitive diagnosis on histology alone and a note describing the diagnostic difficulty is prudent, but a diagnosis can be favored using other softer histologic features. As mentioned previously, GERD typically affects the distal portion of the esophagus, while EoE affects the mid- to upper esophagus. Additional samples from the mid- and upper esophagus can be helpful if they are not included in the initial set of biopsies. The eosinophils in GERD are usually randomly distributed throughout the epithelium, whereas the intraepithelial eosinophils in EoE are most concentrated in the upper portion of the epithelium. Eosinophil degranulation, eosinophil microabscesses, and basal zone hyperplasia are also increased in EoE compared to GERD. Biopsy findings are only one portion of the diagnostic puzzle, and the patient age, sex, medical history, symptomatology, ancillary test results, and response to treatment need to be considered to arrive at an appropriate diagnosis.

In addition to making the diagnosis of EoE, pathologists are frequently asked to provide an eosinophil count in known cases of EoE as a marker of disease severity or treatment response. We typically provide a count in the densest high-power field without additional comment. Comparison to prior biopsies should be taken with care as the size of microscopic fields can vary between microscopes and variably thick fragments of rectangular tissue may fill different quantities of area within a round microscopic field. Known variability in the severity of disease within the esophagus should also prompt caution in over-interpreting response to treatment in any individual patient as there still may be severe disease in unsampled areas. One recent study found that the number of eosinophils in the initial biopsy was inversely correlated with treatment response. Readers who work with resident and fellows should be encouraged as this tedious task has been reported to be highly accurate when performed by trainees.
References: [12, 16, 17, 19–21]

4. Can response to PPI treatment be used to diagnose GERD over EoE?

While response to empiric PPI treatment is used to diagnose GERD in patients with typical symptoms, this delineation between the two diseases is blurred by the recently described "proton pump inhibitor-responsive eosinophilic esophagitis" (PPI-REE). Patient's with PPI-REE have clinical and histologic features that overlap EoE but achieve clinical and histologic remission on PPI therapy. Endoscopic findings have also proven unreliable in distinguishing EoE from PPI-REE. Studies have additionally found that a portion of EoE patients who have responded to traditional EoE therapies (corticosteroids and/or dietary restriction) respond to PPIs and patients with PPI-REE also respond to traditional EoE therapies. Since EoE and PPI-REE cannot

be distinguished clinically, endoscopically, histologically, or by treatment response, many experts believe that they should all fall under the umbrella of EoE and that PPIs should be considered a possible treatment for EoE. To summarize the answer to the original question, response to PPI treatment likely leads to the incorrect diagnosis of GERD in some patients who actually have EoE, but this does not create a major clinical problem as these patients are effectively treated by the PPI.
References: [6, 22–27]

5. Are eosinophils a necessary component to diagnose GERD?

No, while scattered eosinophils aid in the diagnosis of GERD, they are not a sensitive marker and their absence does not exclude the diagnosis. This may especially be the case in acute GERD. Reflux esophagitis is damage to the esophagus caused by the backflow of gastric contents through the gastroesophageal junction into the esophagus. Historically, the damage has thought to have been as a result of mucosal irritation/chemical injury of the hydrochloric acid on the esophageal luminal surface. However, recent studies in both mice and in humans have provided evidence that the damage may be cytokine-mediated. In particular, they have found that biopsies in patients with acute GERD (taken 1 week or 2 weeks after discontinuing PPIs) have increased intraepithelial lymphocytes (mostly T cells). There were very few to no eosinophils or neutrophils in these biopsies of acute GERD.
References: [2, 7–10, 28]

6. Are increased intraepithelial eosinophils in the esophagus only seen in GERD and EoE?

Of course not. Like almost everything else in the esophagus, eosinophils are etiologically nonspecific and can be associated with many different entities. Duodenum and stomach biopsies should be examined to ensure that the biopsy does not represent esophageal involvement of eosinophilic gastroenteritis. Scattered eosinophils can also reflect Crohn disease and collagen vascular disease and as a reaction to medication (Table 2.2). Unfortunately, cases with these complicated systemic diseases are often impossible to parse out. The esophageal changes could be due to the disease itself, medications for the disease, and reflux esophagitis related to decreased motility from the systemic disease, and of course people with systemic diseases can also have GERD just like anyone else. Lastly, large eosinophilic abscesses should raise suspicion for parasites and additional levels should be obtained to exclude their presence.
Reference: [29]

7. What are the clinical and histologic characteristics of lymphocytic esophagitis pattern?

Biopsies from patients with a lymphocytic esophagitis pattern have numerous intraepithelial lymphocytes randomly distributed throughout the epithelium or exhibiting a predilection of peripapillary distribution (Fig. 2.3a–c). As for other forms of esophagitis, reactive epithelial changes are seen with edema and squamous hyperplasia. Rare to no neutrophils or eosinophils should be present. No count of the lymphocytes needs to be performed as the diagnosis is based on the pathologist's opinion that there are too many. The changes are most commonly seen in the distal esopha-

Table 2.2 Entities where intraepithelial eosinophils can be seen

Reflux disease
Eosinophilic esophagitis
Systemic eosinophilic gastroenteritis
Crohn disease
Medication effect
Collagen vascular disease
Parasite (eosinophilic abscess)

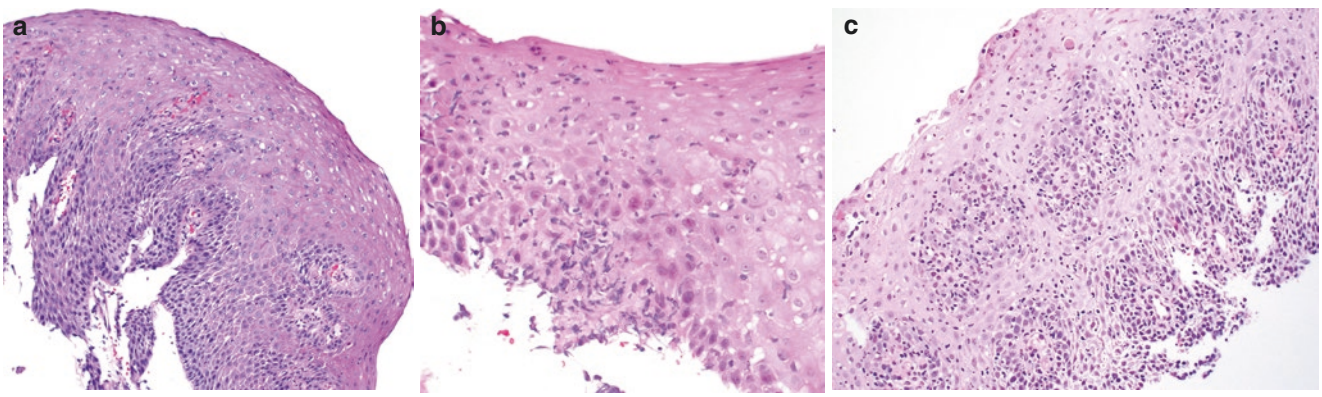

Fig. 2.3 Lymphocytic esophagitis patterns. (**a**, **b**) Squamous epithelium with increased intraepithelial lymphocytes scattered throughout the epithelium, basal layer hyperplasia, and increased papillae height. (**c**) Characteristic peripapillary distribution of intraepithelial lymphocytes can also be seen

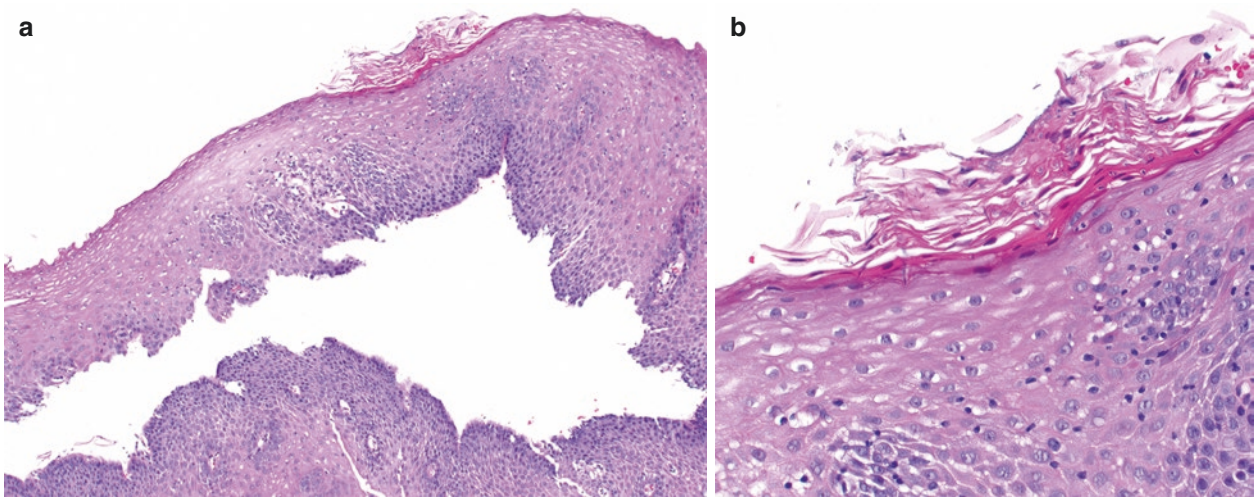

Fig. 2.4 *Candida* esophagitis. (**a**) Focal area of parakeratosis that should raise suspicion for *Candida* infection. (**b**) High-power view showing fungal pseudohyphae mixed with keratin debris compatible with *Candida*

gus but can also affect the mid- and proximal portions. As this is a nonspecific pattern, other more specific forms of esophagitis should be considered. Reflux esophagitis can be lymphocyte-predominant and cannot be excluded on histologic grounds alone. Acid pH monitoring and response to PPI therapy can be used to exclude this possibility. *Candida* esophagitis should also be considered, but it typically has a superficial neutrophilic infiltrate with sloughed off keratin debris with intermixed fungal forms (Fig. 2.4a, b). A range of endoscopic findings can be seen. The esophagus can appear normal or just have mild erythema, but it can also have plaques, rings, strictures, or furrows. The pattern is rare as it was diagnosed in approximately 0.1% of biopsies in one large study of adults. The median age of the patients with lymphocytic esophagitis was 63 and 60% were women. The pattern was more common in a study from a pediatric medical center where it was seen in just over 5% (31/545) of patients. The most common symptoms are dysphagia and reflux symptoms. In the original description of 20 cases with this pattern from 2006, the patients had a range of associated disorders including reflux disease, Crohn disease, Hashimoto thyroiditis, cirrhosis, gastroduodenitis and ulcer, celiac disease, carcinoma, and hiatal hernia, and some patients were asymptomatic. Later studies have also shown a wide range of associations but the majority of cases are idiopathic. Crohn disease has been associated with lymphocytic esophagitis in children, but this is not reproduced in adults. Lymphocytic esophagitis pattern was not increased compared to controls in patients with ulcerative colitis. Some studies have reported this pattern in association with esophageal motility disorders and in Barrett esophagus patients with high-grade dysplasia after ablation therapy.

References: [30–40]

8. What are the clinicopathologic characteristics of lichenoid esophagitis?

A lichenoid esophagitis pattern consists of a dense T-cell-rich lymphocytic infiltrate concentrated at the junction of the squamous epithelium and lamina propria with degeneration of the basal epithelium. Scattered degenerated squamous cells with bright eosinophilic cytoplasm can be seen that are akin to Civatte bodies in lichen planus of the skin (Fig. 2.5a, b). As opposed to lichen planus of the skin, which shows hypergranulosis and orthokeratosis, lichenoid esophagitis typically shows parakeratosis and lacks hypergranulosis since the normal esophageal epithelium lacks a granular layer. Also, rather than being acanthotic, lichenoid esophagitis is usually atrophic but can show areas of either atrophy or acanthosis. Esophageal involvement by lichen planus can be differentiated from lichenoid esophagitis pattern through clinical history of mucocutaneous lichen planus or through direct immunofluorescence (DIF). DIF shows round deposits of IgM at the junction of the squamous epithelium and lamina propria. There is some overlap in features between lichenoid esophagitis and lymphocytic esophagitis. While the distinction can be difficult, Civatte bodies have not been described in lymphocytic esophagitis, and it also typically lacks striking apoptosis and band-like inflammation at the junction of the squamous epithelium and lamina propria. The upper, mid-, and lower esophagus can all be affected.

Lichenoid esophagitis is a pattern of injury that is akin to lichen planus in the skin. This pattern does in fact include cases of esophageal involvement of lichen planus, but this pattern is also seen in a variety of clinical settings in the esophagus. Lichen planus is a mucocutaneous inflammatory disease that can affect the skin, nails, oral and genital mucosa, and the esophagus. The mecha-

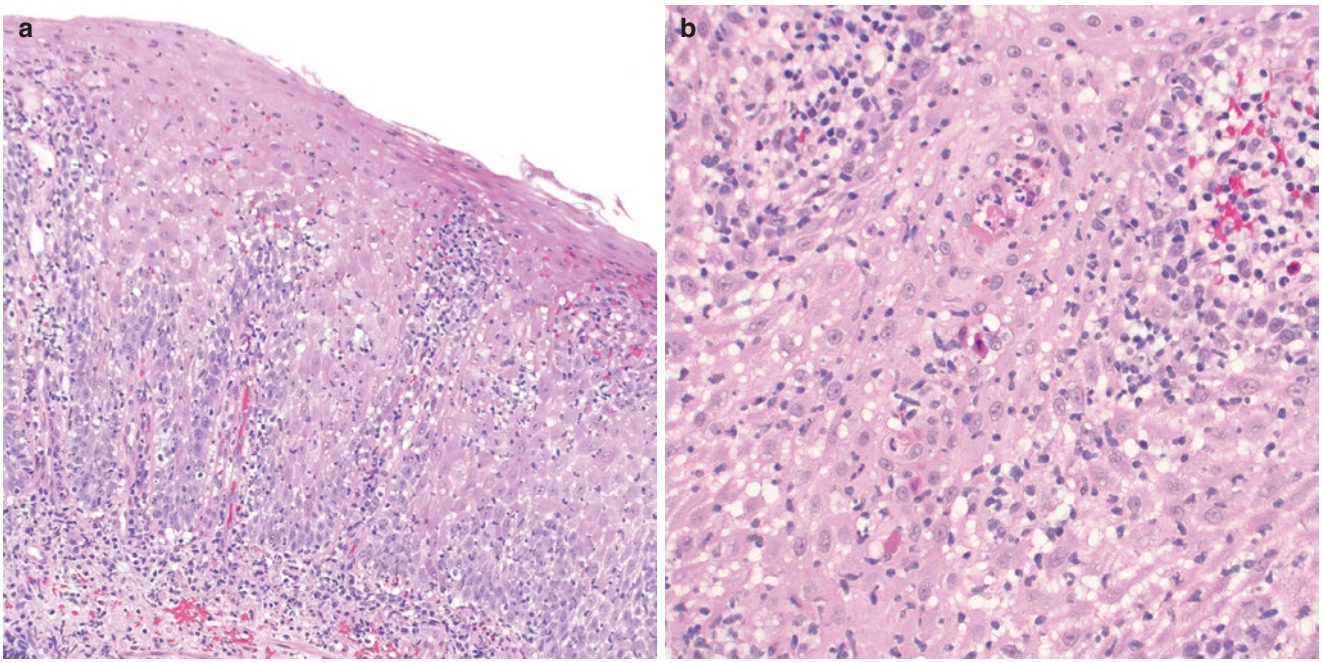

Fig. 2.5 Lichenoid esophagitis pattern. (**a**) Markedly increased lymphocytes most concentrated at the junction of the base of the epithelium and lamina propria. There are also basal layer hyperplasia and intercellular edema. (**b**) Highlights a dyskeratotic cell compatible with a Civatte body

nism of disease is not fully understood, but it can be triggered by allergic disease and hepatitis C viral infection. The condition consists of purplish, flat bumps on the skin that can form blisters that can crust or scab. White plaques can form on mucosal surfaces. Patients with esophageal disease can present with dysphagia and strictures. Endoscopic findings can include stricture and peeling, friable mucosa that can be difficult to distinguish from eosinophilic esophagitis. A large case series of 88 specimens from 65 patients with lichenoid esophagitis pattern was conducted at Johns Hopkins Hospital. These patients were predominantly females in their 50s or 60s. About a third (32%) of the patients had confirmed lichen planus. Of the patients without lichen planus, 59% were taking at least four medications, 23% had a chronic viral disease (HIV or viral hepatitis), 11% had an associated rheumatologic disorder, and 7% progressed to dysplasia or carcinoma. Patients with lichen planus were more likely to have a stricture than those without (38% versus 9%). Table 2.3 details a comparison between lymphocytic and lichenoid esophagitis patterns.
References: [41–44]

Table 2.3 Clinicopathologic comparison of lymphocytic and lichenoid esophagitis patterns

	Lymphocytic esophagitis	Lichenoid esophagitis
Age	60s	50s or 60s
Symptoms	Dysphagia, reflux symptoms, can be asymptomatic	Dysphagia, reflux symptoms, can be asymptomatic
Disease associations	Majority idiopathic, GERD, Crohn, Hashimoto, cirrhosis, celiac disease, gastroduodenitis, carcinoma, esophageal motility disorders, Barrett esophagus s/p ablation for dysplasia	Lichen planus, polypharmacy, chronic viral disease (e.g., viral hepatitis or HIV), rheumatologic disease
Intraepithelial lymphocytes	Randomly distributed throughout epithelium or peripapillary	Concentrated at junction of epithelium and lamina propria
Additional histologic findings	Intercellular edema, squamous hyperplasia, ballooning keratinocytes. Lacks Civatte bodies and apoptosis	Civatte bodies, degeneration of basal epithelium with apoptosis, parakeratosis, atrophic or acanthotic
Location	Distal most common, but can also affect mid and proximal	All levels

9. What are the causes and long-term implications of corrosive injury to the esophagus?

Corrosive injury of the esophagus is injury that occurs due to ingestion of lye or another caustic substance. These injuries are very sad as they most commonly result from either accidental ingestion by a young child or a suicide attempt. Grossly there are necrosis and extensive internal hemorrhage (Fig. 2.6a, b). Patients with acute ingestions are rarely biopsied, but acute inflammation and necrosis are seen in a pattern similar to that seen in sloughing

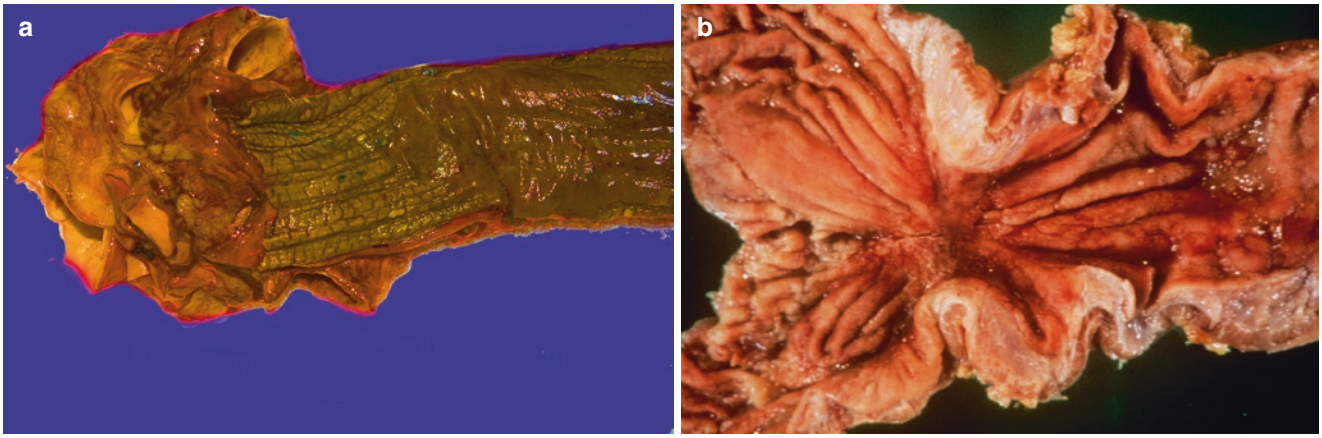

Fig. 2.6 Corrosive ingestion. (**a**) Gross photograph of an esophagus following intentional (suicide) lye ingestion shows diffuse necrosis with extensive internal hemorrhage. (Photograph courtesy of Dr. Priya Banerjee). (**b**) Gross photograph showing ulceration in the stomach following hydrochloric acid ingestion

esophagitis. Chronic lesions typically show full-thickness fibrosis on the esophageal wall that corresponds with an endoscopically apparent stricture and prolonged transit time of food through the esophagus. Importantly, these patients need to undergo lifetime surveillance as they are estimated to have a thousandfold increased lifetime risk of squamous cell carcinoma. Follow-up needs to be long-term as there can be a 40-year latency period before cancer development.

References: [45–49]

10. How are the most common types of pill fragments in pill esophagitis histologically distinguished?

Pill-induced esophagitis is a common cause of injury that refers to injury due to contact between the pills and the esophageal mucosa. It is frequently associated with erosion and ulceration and most commonly affects the mid-esophagus. Oftentimes no pill or just nonspecific polarizable material is seen. The squamous mucosa often shows erosion or ulceration with fibrinopurulent debris. At times, the squamous mucosa can have a sloughing (esophagitis dissecans superficialis) pattern of injury. Marked reactive epithelial and stromal reactive changes can be seen that should not be misdiagnosed as dysplasia or malignancy. Multinucleated squamous giant cells can also be seen. Fungal forms and viral cytopathic effect should be excluded. Treatment includes PPIs, sucralfate, withdrawal of the offending medication, and behavioral modification such as sitting upright while ingesting the medication. In instances for which the biopsy findings are nonspecific, clinical correlation and the establishment of a temporal relationship with the drug are necessary. Among others, NSAIDs, bisphosphonates, and doxycycline are common causes of esophageal injury for which no specific pill fragment is seen. There are, however, certain injurious medications that produce specific microscopic appearances.

Injury due to iron pills is generally seen in the upper gastrointestinal tract, and iron pill esophagitis is not uncommonly seen by practicing pathologists. Iron supplements are most commonly taken in the setting of iron deficiency anemia. They can cause an erosive/ulcerative injury with dark purple or brown-black crystalline material in granulation tissue or fibrinopurulent debris (Fig. 2.7a–d). The iron fragments can be highlighted by iron stain if necessary. The ulceration can cause marked reactive epithelial and stromal changes that should not be mistaken for dysplasia or malignancy.

Pill fragments from three types of resins (kayexalate, sevelamer, and bile acid sequestrants) have been identified in the gastrointestinal tract. While all three are more commonly seen at other sites, they are all rarely identified within the esophagus. Kayexalate (sodium polystyrene sulfonate) is a cation exchange resin used to treat hyperkalemia. It was originally described in the pathology literature as a cause of gastrointestinal injury in a series of five cases of colonic necrosis in 1987. Subsequent case series describing kayexalate effects in the gastrointestinal tract have included cases with active esophagitis, esophageal ulcer, and esophageal squamous carcinoma. Importantly the background squamous epithelium needs to be carefully examined as both series included a patient with herpes esophagitis and another coinfected with *Candida*. While it seems that kayexalate can cause damage to the gastrointestinal tract independent of additional insults, it is unclear whether it potentiates the ulceration caused by herpes simplex virus (HSV) or is a passenger in these situations. In addition to the original descriptions, the morphology of

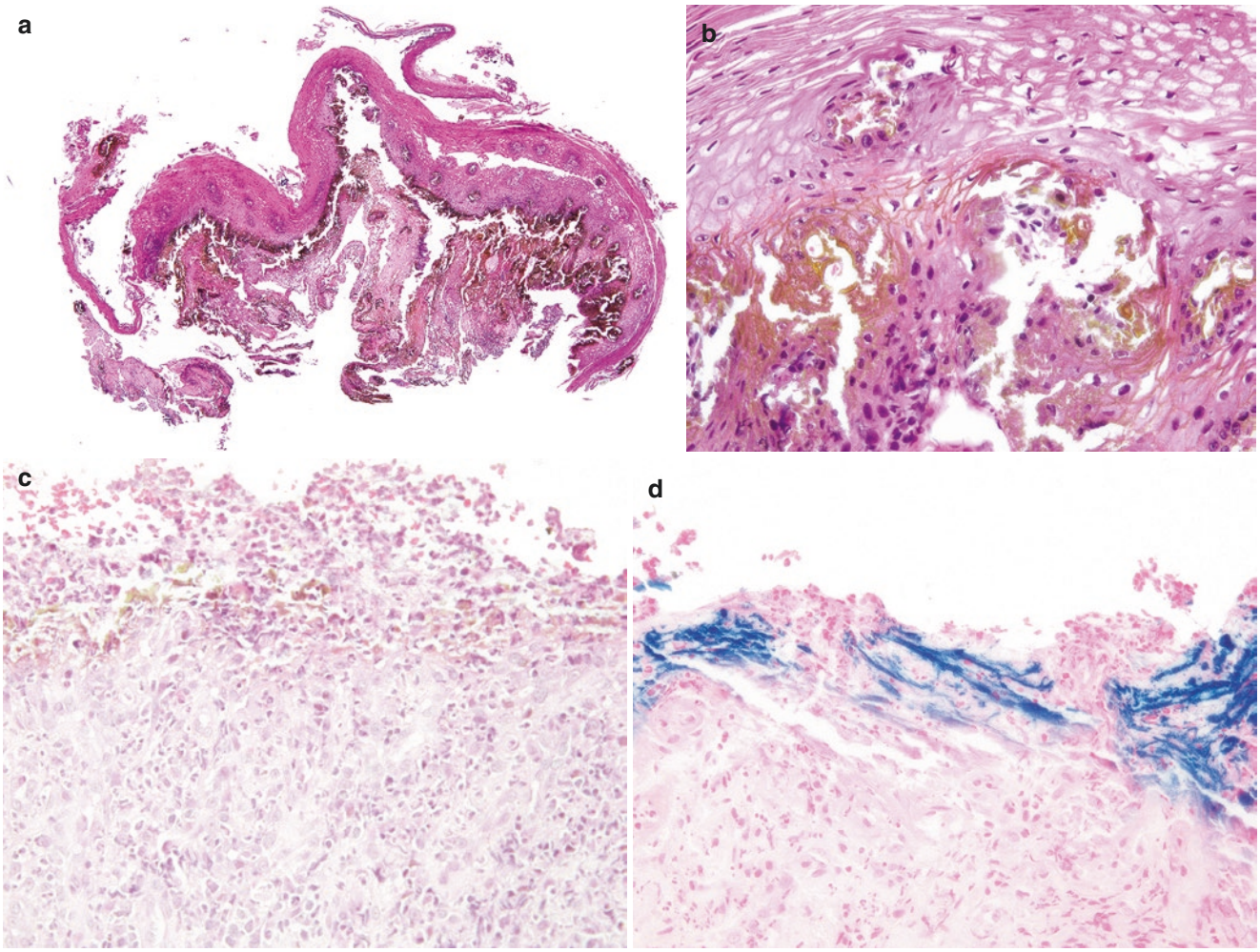

Fig. 2.7 Iron pill esophagitis. (**a**) Low-power view shows reactive squamous mucosa with abundant brown pigment compatible with iron at the base of the epithelium. (**b**) High-power view of light-brown iron pigment crystals at the base of the epithelium. (**c**) Ulcerated esophagus with light-brown iron pigment at the surface. (**d**) Iron stain (blue) confirms the diagnosis of iron pill esophagitis

crystal resins seen in the gastrointestinal tract has been expertly described and compared in great detail in a recent review. Kayexalate crystals are rectangular purple crystals with evenly spaced fish scales (Fig. 2.8a–c). On AFB stain the crystals are black. Confirmation with clinical history is vital as these histologic features can vary depending on the site within the gastrointestinal tract and the various crystals can be mistaken for other types of pill fragments or even dystrophic calcifications.

Sevelamer (Renagel, Renvela) is an anion exchange resin used to decrease phosphate in patients with chronic kidney disease. It was first associated with injury to the gastrointestinal tract in a case series from 2013. One of the seven cases involved the esophagus, which showed extensive circumferential erosions and ulcerations with a thick white exudate. Sevelamer crystals are typically rectangular and "two-toned" in color with bright-pink center and background rusty-yellow edges. One should take caution in relying on color as it can be variable and even look purple like kayexalate. The fish scales in sevelamer crystals are typically wide and irregularly distributed. On AFB stain, sevelamer crystals are magenta. Again, a clinical history can be invaluable to confirming their identity.

Bile acid sequestrants (BAS; including cholestyramine, colesevelam, and colestipol) are used to treat hypercholesterolemia and hyperlipidemia. One large case series of pill fragments in the gastrointestinal tract found them in the esophagus in just 1 of the 25 cases. They can be found in the lumen and within the tissue. Their association with mucosal injury is not well established. The three bile acid sequestrants are histologically indistinguishable. They are polygonal with a homogenous pink color and lack the fish scales seen in kayexalate and sevelamer fragments. On AFB stain they are pale yellow in color.

References: [50–60]

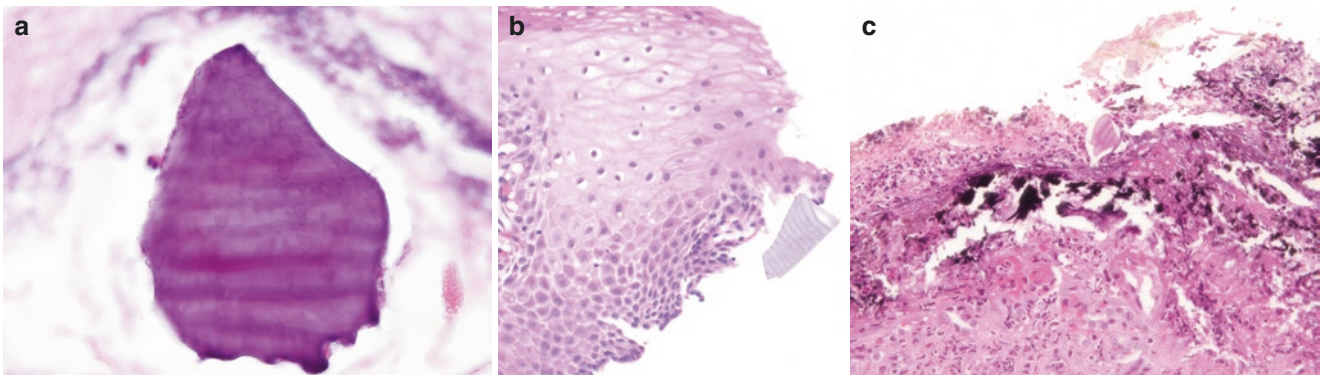

Fig. 2.8 Kayexalate. (**a**) High-power view of a kayexalate crystal with the classic homogenous purple color and evenly distributed fish scales. (**b**) Kayexalate crystal on the right shows homogenous pale purple color and even distributed fish scales. In this case the resin was detached and there was no associated injury in the esophagus. (**c**) A case of erosive esophagitis with two potential offending agents. Brown-black iron pigment and purple kayexalate crystals

11. What other medications cause morphologic changes in the esophagus?

Taxanes are chemotherapeutic agents that bind to microtubules and inhibit depolymerization. They are commonly used to treat carcinoma of the esophagus, breast, and lungs. Marked mucosal changes with prominent mitotic arrest with ringed mitoses and prominent apoptotic bodies due to taxanes were first described in the esophagus in 1989 during initial phase I clinical trials of Taxol. A subsequent large case series described these changes in biopsies throughout the gastrointestinal tract. These dramatic epithelial changes can closely mimic high-grade dysplasia. These changes have not been associated with toxicity, and these changes are thought to be manifestations of the drug's intended mechanism of action.

Colchicine is an alkaloid with antimitotic activity used to treat flares of gout and to prevent attacks of abdominal, chest, and joint pains by familial Mediterranean fever. One case series of colchicine effects in the gastrointestinal tract did not include any cases with esophageal findings, but older studies have reported esophageal injury. Symptoms are nonspecific but can entail abdominal pain, diarrhea, and cramping. Endoscopic findings include inflammation and erosion/ulceration. Similar to those seen in association with taxanes, histologic findings include increased metaphase (ringed) mitoses, increased apoptotic bodies, and reactive epithelial changes. Unlike for taxanes, these changes are only seen with clinical toxicity and are not present with therapeutic drug levels.

Mycophenolate (CellCept or Myfortic) can also induce injury to the upper gastrointestinal tract. It is an immunomodulatory drug used in autoimmune diseases such as systemic lupus erythematosus (SLE) and to prevent rejection in organ transplant recipients. Gastrointestinal symptoms include diarrhea, nausea and vomiting, abdominal pain, dysphagia, and gastrointestinal bleeding. In one series, four of the six evaluable biopsies in the esophagus showed increased apoptotic bodies (Fig. 2.9a, b). Additional findings included active inflammation, erosion, and ulceration. Graft-versus-host disease (GVHD) can be difficult to differentiate from mycophenolate toxicity as both feature increased apoptosis. Clinical information is key as GVHD occurs in stem cell transplants, while mycophenolate is most often used in solid organ transplant recipients, but there are times when a stem cell transplant recipient is given mycophenolate. While there are no reliable features to distinguish mycophenolate toxicity from GVHD in the esophagus, increased adjacent eosinophils are more commonly seen with mycophenolate toxicity in other areas of the gastrointestinal tract. Lastly, cytomegalovirus (CMV) infection should also be excluded in this setting as it often features acute inflammation, ulceration, and increased apoptotic bodies and immunocompromised patients are more prone to this opportunistic infection.

Ipilimumab is a monoclonal antibody directed against cytotoxic T-lymphocyte antigen-4 (CTLA-4) that is used to treat various malignancies. It, along with other immune checkpoint inhibitors (PDL-1), has been associated with gastroenteritis with diarrhea. While, to our knowledge, these medications do not typically produce esophageal injury, one anecdotal case seen at Johns Hopkins showed prominent apoptosis, increased intraepithelial lymphocytes, and marked reactive epithelial changes with basal cell hyperplasia, intercellular edema, and keratinocyte vacuolization.

References: [61–71]

12. What are the features of sloughing esophagitis/esophagitis dissecans?

Sloughing esophagitis (esophagitis dissecans superficialis) is a condition in which a superficial portion of the esophageal epithelium sloughs off or splits from the

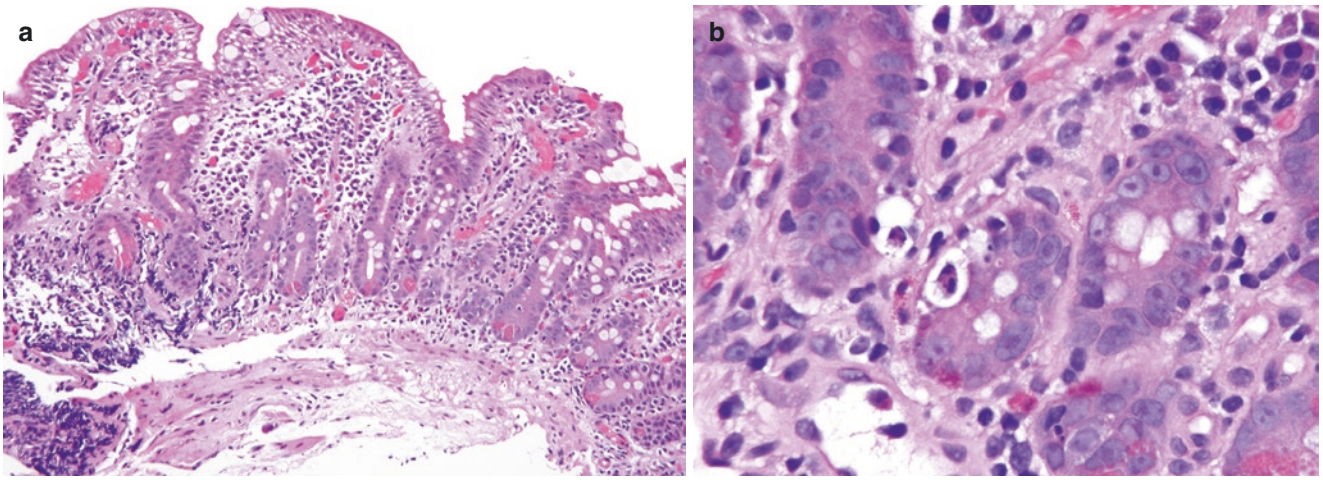

Fig. 2.9 Mycophenolate toxicity. (**a**, **b**) Although these photographs are from the small bowel, they highlight the markedly increased apoptotic bodies, scattered surrounding eosinophils, villous shortening, and epithelial reactive changes that can be seen with mycophenolate toxicity

underlying epithelium. This is seen on endoscopy as single to numerous white patches or a single large white tube of sloughed off mucosa (Fig. 2.10a). This impression is confirmed on histology with a well-delineated, often with splitting above the basal layer, superficial strip of parakeratosis and necrosis (Fig. 2.10b–e). There is typically very little inflammation. Immunohistochemical study has not found any aberration in integrin expression. Immunofluorescence studies have shown no C3 or immunoglobulin deposits. Usually the mid- or distal esophagus is affected. Symptoms can include dysphagia possibly with stricture, gastrointestinal bleeding, weight loss, epigastric pain, and most severely can result in vomiting of tubes of mucosa, but the disease can also be asymptomatic. Like so many other inflammatory conditions in the esophagus, sloughing esophagitis is also a nonspecific pattern of injury. Patients are typically middle-aged to elderly and the pattern of injury is more common in men. Studies have shown an association with some medications including NSAIDs, bisphosphonates, psychoactive medications, and polypharmacy in general. Risk factors include debilitation, immunosuppression, smoking, and physical trauma (e.g., drinking hot beverages).

References: [72–78]

13. What are the diagnostic features of and the differential diagnosis for pemphigus vulgaris (PV)?

Pemphigus vulgaris is a dermatologic condition that, like lichen planus mentioned previously, can affect the esophagus. It is characterized by intraepithelial splitting just above the basal layer (suprabasal) of the squamous epithelium with acantholytic squamous epithelial cells, bullet-shaped nucleoli, and intercellular edema (Fig. 2.11a–d). Direct immunofluorescence (DIF) is key to differentiating the bullous diseases, and an additional request for fresh tissue can be very helpful. In PV, DIF shows homogenous staining of IgG in the intercellular spaces of the perilesional squamous tissue. These antibodies are generally against desmoglein 1 and/or 3. PV is the most common form of pemphigus and most commonly occurs in patients between 30 and 50 years and has no gender predilection. Oral lesions are almost always seen, but any mucosal surface can be affected. Esophageal involvement is almost always found when endoscopy is performed. Dysphagia and odynophagia (painful swallowing) are the most common esophageal symptoms. Once the diagnosis is made, patients are typically treated with steroids and immunomodulatory agents.

Other bullous dermatologic diseases can also less commonly affect the esophagus. Bullous pemphigoid (BP) principally affects the skin in people age 40–70 years old but can rarely affect mucosal surfaces including the esophagus. BP causes a subepidermal split with prominent eosinophils. It is caused by IgG autoantibodies to hemidesmosomal antigens (BP230 and BP180).

Epidermolysis bullosa includes a variety of rare bullous diseases that affect the skin and mucosal surfaces, and the esophagus is among the most common mucosal sites affected. The most common types are dystrophic epidermolysis bullosa (DEB), epidermolysis bullosa simplex (EBS), and junctional epidermolysis bullosa (JEB). The inherited forms of these diseases are caused by mutations to genes encoding structural proteins (type VII collagen, α6βintegrin, cytokeratins 5 and 14, and laminin), while the acquired version has been associated with various viral infections and autoimmune diseases. All forms are characterized by blister formation caused by minor trauma at skin and mucosal locations. Disease

severity ranges from minor to severe with ulceration, scarring, strictures, and contractures. Lesions (predominantly described in the skin) show splitting in the dermis (DEB), epidermis (EBS), or dermoepidermal junction (JEB). Table 2.4 highlights clinical and pathologic differences between the bullous entities described above.

References: [79–92]

14. How can I figure out the cause of an esophageal ulcer?

The truth is that there are many causes of ulceration that all result in inflamed squamous mucosa with associated granulation tissue and fibrinopurulent debris. As detailed above, some medications can be identified on H&E, but in most cases the pathologist can only report that there is acute erosive esophagitis and maybe sug-

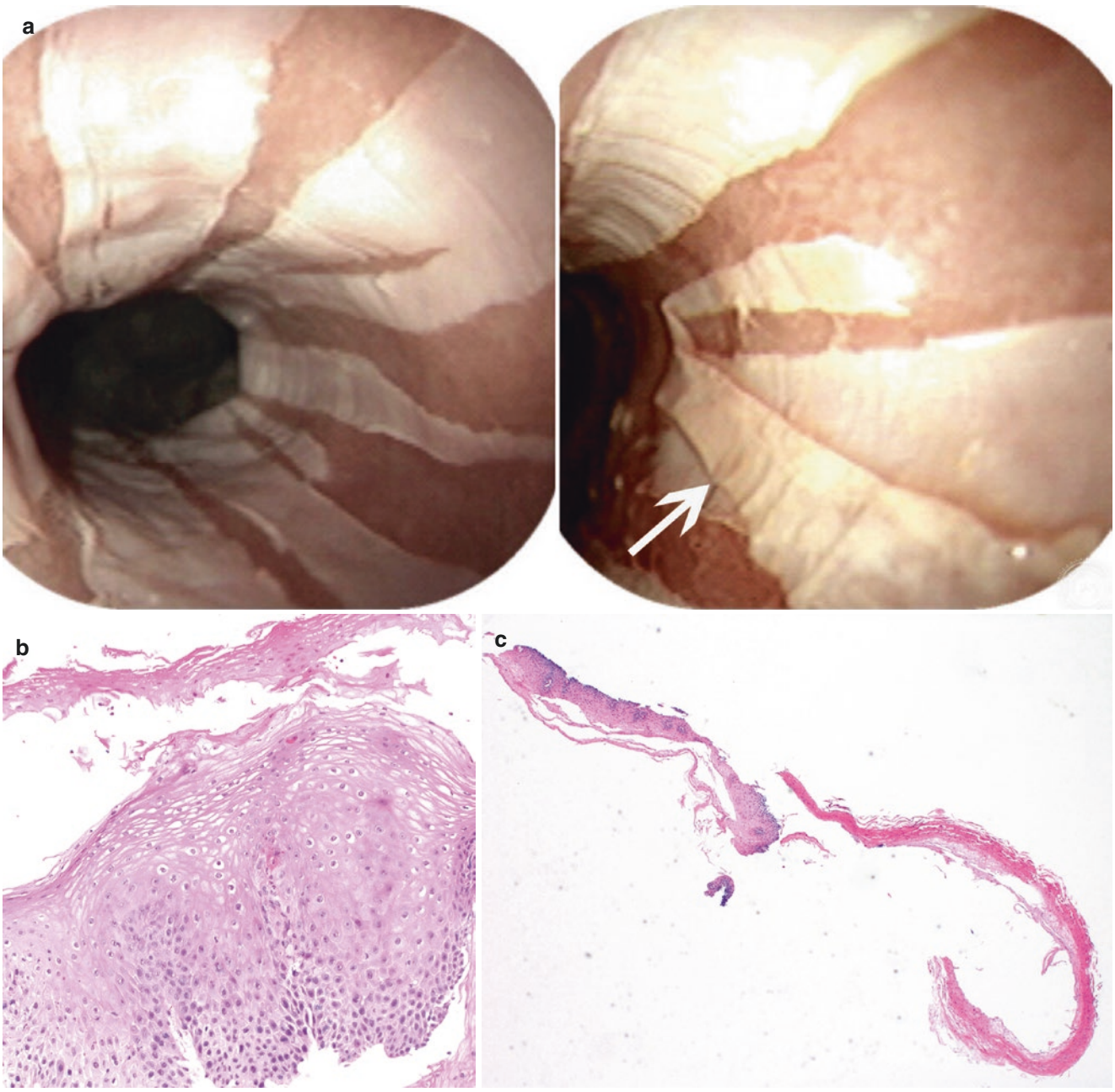

Fig. 2.10 Esophagitis dissecans superficialis. (**a**) Endoscopic examination of the esophagus showing whitish strips of detached squamous epithelium that are dislodged with water spray (white arrow). (**b**, **c**) Medium- and low-power view of squamous mucosa with detached layer of sloughed off superficial epithelium with parakeratosis. (**d**) High-power view of squamous epithelium with distinct superficial layer of parakeratosis with necrosis. Notice the mild acute inflammation. (**e**) High-power view of the classic detached strip of superficial squamous epithelium with parakeratosis, necrosis, and little to no inflammation

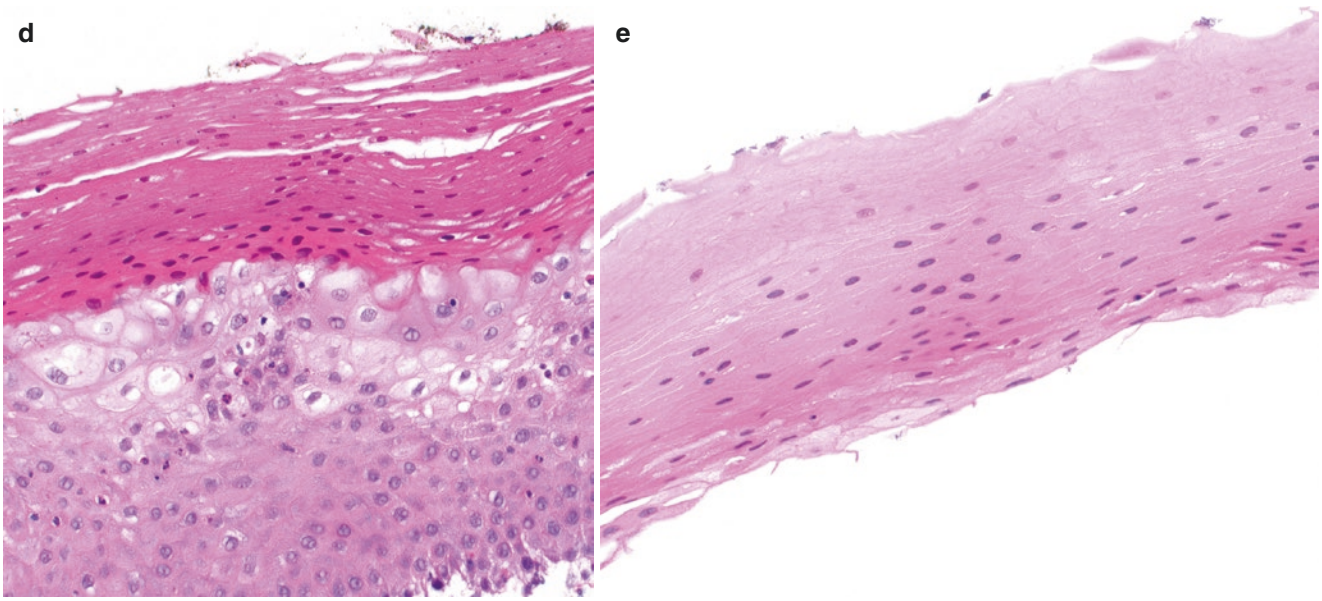

Fig. 2.10 (continued)

gest a cause based on the patient's clinical history and list of medications. The key is actually to exclude causes of ulceration that can either be treated or will drastically change the patient's prognosis and treatment plan.

It is important to exclude malignancy as this diagnosis will have a major impact on the patient. Tumors of the esophagus are covered in detail in a separate chapter, but a neoplastic process should be considered whenever there is ulceration. In addition to primary tumors, metastatic tumors growing up through the muscularis propria can cause ulceration in the overlying mucosa. Even benign tumors like a granular cell tumor in the lamina propria can cause overlying pseudoepitheliomatous hyperplasia or ulceration.

Treatable infections need to also be excluded in esophageal ulceration. HSV only infects epithelial cells, and its inclusions are found in the squamous epithelium immediately adjacent to the ulcer bed and consist of the "three Ms" (multinuclear, margination, and nuclear molding). CMV can infect epithelial cells, endothelial cells, and fibroblasts so its inclusions can be seen both in the epithelium and in the ulcer bed itself. While a careful scan for viral cytopathic effect is prudent in any esophageal ulceration, one should be extra careful in biopsies from immunocompromised patients (e.g., transplant recipients, chemotherapy administration, HIV infection). While not mandatory for each ulceration, immunohistochemical stains for CMV and HSV can be helpful if there are equivocal inclusions on H&E or a strong clinical suspicion. While it often does not cause ulceration, *Candida* esophagitis should also be excluded. Endoscopists are usually quite adept at picking up *Candida* infection as a white plaque, but this may be obscured if there is significant ulceration. The organisms can be visualized as a mixture of pseudohyphae and yeast buds that are most easily picked up in keratin debris of desquamated surface epithelium. Additional histologic findings that should raise suspicion for *Candida* infection are acute inflammation in the squamous epithelium, keratin debris in the luminal space above the epithelium, or lymphocytosis. Again, a careful check should be made in immunocompromised patients, and PAS or GMS special stains can be utilized to help identify organisms.

Case Presentation

Case 1

Learning Objectives

- To learn the differential diagnosis of a large ulcerated lesion
- To exclude identifiable etiologies that are either treatable or confer major prognostic implications
- Two processes and findings can occur simultaneously

Case History

A 71-year-old female with immunosuppression and chronic kidney disease presents with gastrointestinal bleeding.

Endoscopic Findings

Ulcerated necrotic-appearing mass-like area spanning 10 cm of the distal esophagus.

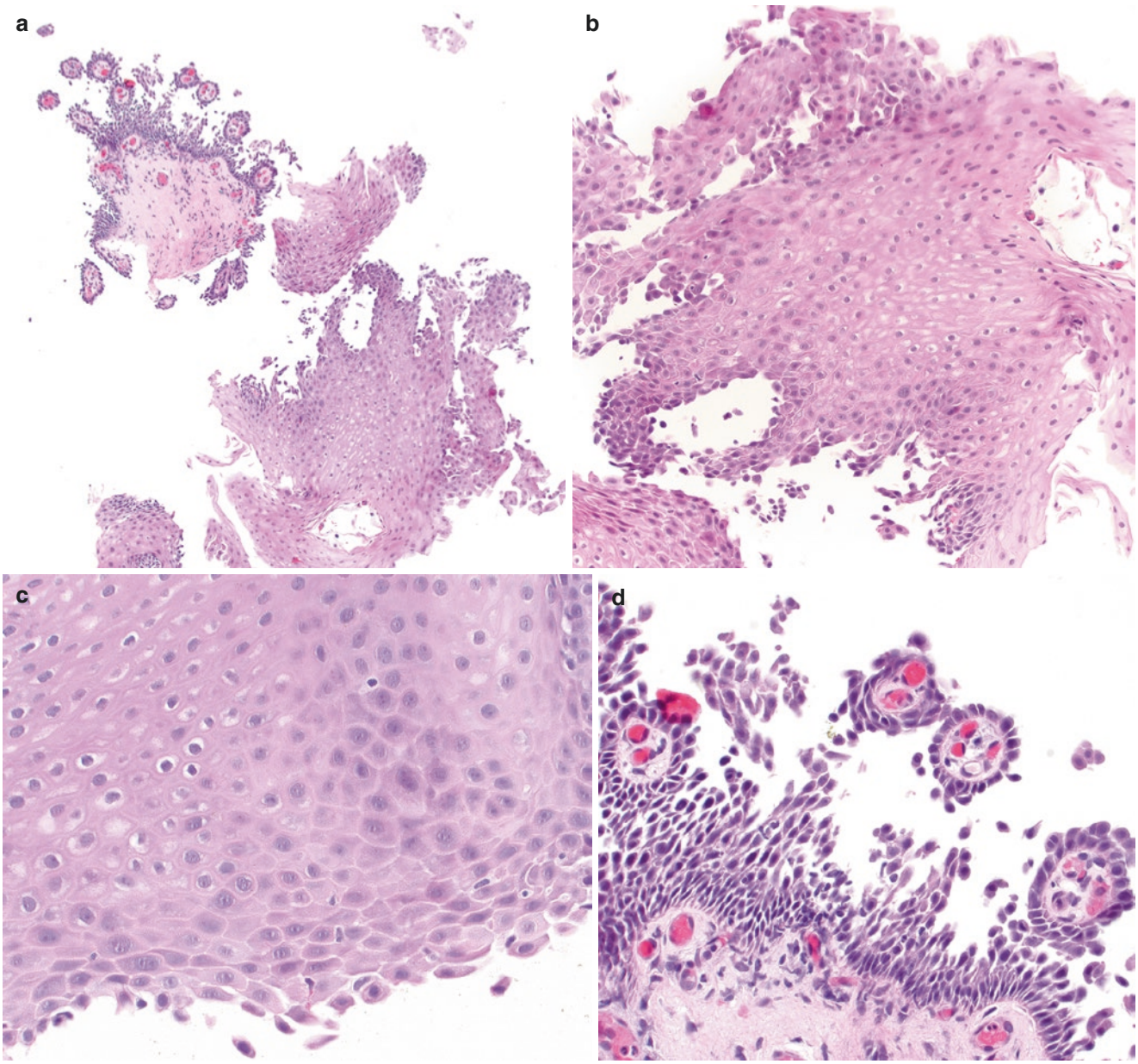

Fig. 2.11 Pemphigus vulgaris. (**a**) Low-power view of a biopsy shows suprabasal clefting of the squamous epithelium. (**b**) Squamous epithelium shows partial loss of the basal layer with acantholysis and mild intercellular edema with little to no inflammation. (**c**) High-power view highlights the "bullet-shaped" nucleoli in the reactive squamous cells. (**d**) Lamina propria and papillae have a layer of remaining basal cells with the hallmark "tombstone" appearance

Differential Diagnosis Prior to Slide Review

- Malignancy
- Virus
- Medication effect
- GERD
- Toxic ingestion

Histologic Findings

- Necroinflammatory debris with numerous pill fragments, bacteria, and foodstuff (Fig. 2.12a, b).
- Numerous crystals with a variety of morphologic appearances. Most were pink with wide irregular fish scales and slightly rust-colored edges. However, some were purple in color, while others lacked fish scales (Fig. 2.12c–e).
- Rare degenerated squamous epithelium with areas where the nuclei were molded with marginated chromatin and multinucleation (Fig. 2.12f).

Differential Diagnosis After Slide Review

- Pill fragments
  - Sevelamer
  - Kayexalate
  - Cholestyramine
  - Others

Table 2.4 Comparison of pemphigus vulgaris with bullous pemphigoid and epidermolysis bullosa

	Pemphigus vulgaris	Bullous pemphigoid	Epidermolysis bullosa
Commonly affects the esophagus	Yes	No	Yes
Esophageal symptoms	Dysphagia, odynophagia	Dysphagia, odynophagia	Dysphagia, odynophagia
Cause	Antibodies to desmoglein 1 and/or 3	Antibodies to hemidesmosomal antigens (BP230 and BP180)	Inherited form: Mutations to structural proteins Acquired form: Viral infection or autoimmune diseases
Level of split	Suprabasal with clinging basal layer with "tombstone" appearance	Subepidermal	Epidermis (EBS) Dermis (DEB) Epidermal/dermal junction (JEB)
Additional histologic findings	Intercellular edema, bullet-shaped nucleoli, mild to no inflammation	Prominent eosinophils	Little to no mixed inflammation
DIF	Intercellular IgG and C3 in lower basal aspect of the epidermis with "chicken-wire" pattern	Linear deposition of IgG and CE at junction	Altered staining pattern at level of molecular defect

- Virus
  - Herpes esophagitis
  - CMV

IHC and Other Ancillary Studies
- Pill fragments are magenta on AFB special stain.
- Degenerated squamous cells are immunoreactive for HSV I immunostain (Fig. 2.12g).

Final Diagnosis
Herpes esophagitis with sevelamer crystals (confirmed by reconciliation with medication list).

Take-Home Messages
- Sevelamer crystals are associated with mucosal injury in the gastrointestinal tract.
- They can have a variable morphologic appearance and be mistaken for other pill types when they have a purple color (kayexalate) or lack fish scales (cholestyramine).
- Underlying viral esophagitis should be carefully examined for and excluded in cases of pill esophagitis.

Case 2

Learning Objectives
- Lichenoid esophagitis is a pattern of injury that is not specific to any single etiology
- A portion of cases are manifestations of lichen planus, but others are associated with viral infections and polypharmacy

Case History
A 51-year-old male with dysphagia and a history of hepatitis B infection.

Endoscopic Findings
Inflammation and scattered ulcers.

Differential Diagnosis Prior to Slide Review
- GERD
- EoE
- Lymphocytic esophagitis
- Lichenoid esophagitis
- Medication effect

Histologic Findings
- Squamous mucosa with dense lymphocyte-predominant inflammation concentrated in band-like pattern at the base of the epithelium and lamina propria (Fig. 2.13a).
- Scattered Civatte bodies (Fig. 2.13b).

Differential Diagnosis After Slide Review
- Lichenoid esophagitis
- Esophageal involvement of lichen planus
- Lymphocytic esophagitis
- GERD

IHC and Other Ancillary Studies
- DIF to rule out lichen planus. Negative for round deposits of IgM at the junction of the squamous epithelium and lamina propria.

Final Diagnosis
Lichenoid esophagitis pattern possibly associated with the patient's viral hepatitis.

Take-Home Messages
- Lichenoid esophagitis pattern of injury can be associated with esophageal involvement of lichen planus, viral infection, polypharmacy, and rheumatologic diseases.

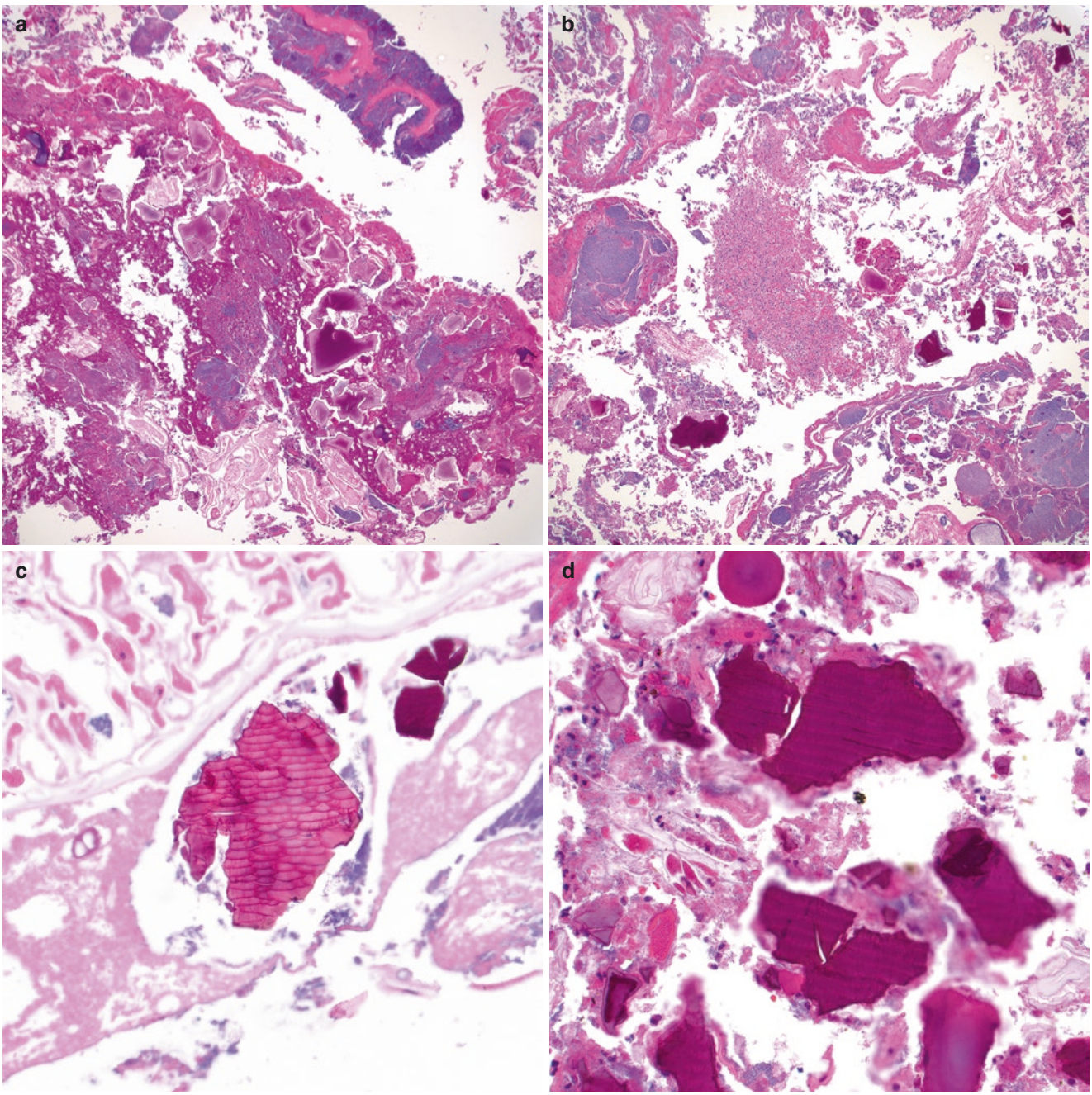

Fig. 2.12 Case 1. (**a**, **b**) Numerous sevelamer crystals mixed in a background of necroinflammatory debris, bacterial colonies, and foodstuff. The crystals show variable morphology throughout the material with some showing (**c**) the typical pink color with rust-colored edges and wide irregular fish scales, while others (**d**) are purple in color raising the differential of kayexalate, and others (**e**) lack fish scales. (**f**) Mixed in the debris are detached degenerated squamous cells showing multinucleation, nuclear molding, and chromatin margination compatible with herpes viral cytopathic effect. (**g**) An HSV I immunohistochemical stain clinched the diagnosis

- While difficult to distinguish from lymphocytic esophagitis, lichenoid esophagitis is more likely to feature band-like inflammation centered at the junction of the base of the epithelium and lamina propria and Civatte bodies.

Case 3

Learning Objectives

- Intraepithelial eosinophils are not limited to reflux esophagitis and eosinophilic esophagitis

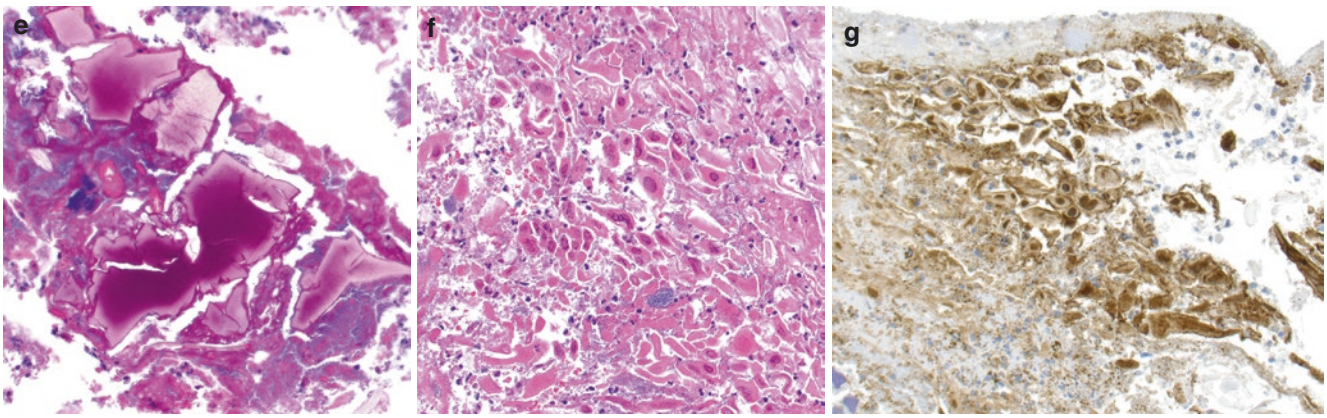

Fig. 2.12 (continued)

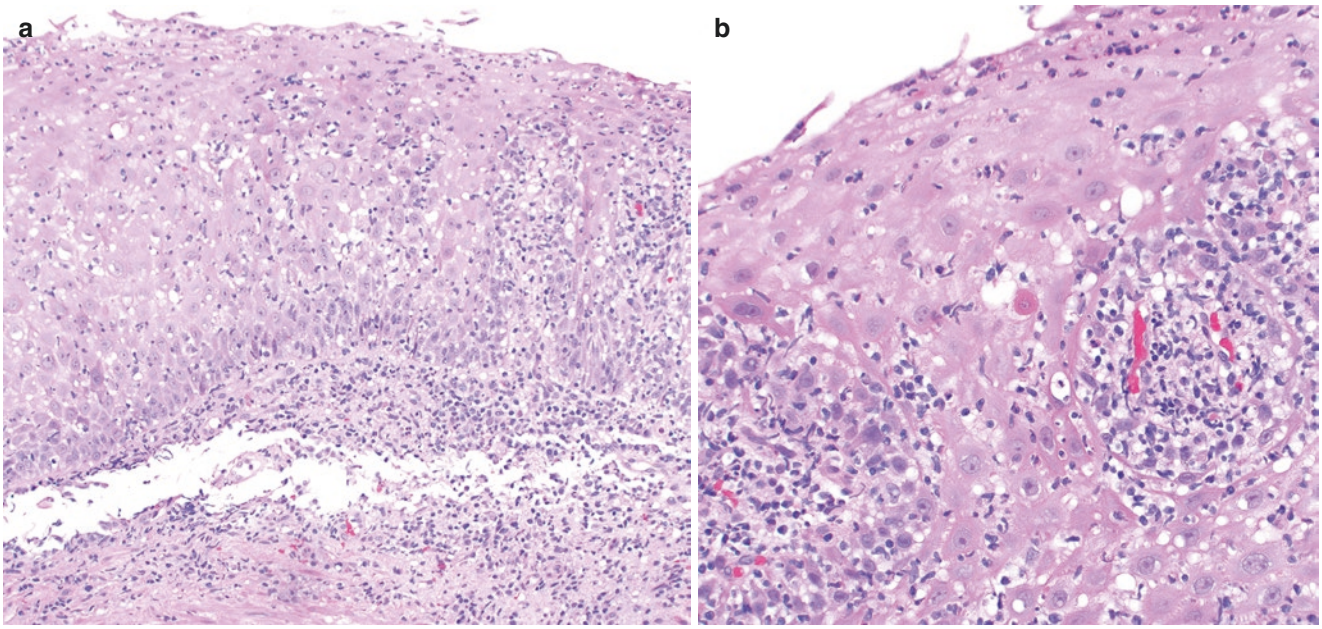

Fig. 2.13 Case 2. (**a**) Dense band-like lymphocytic inflammation most concentrated at the base of the epithelium and lamina propria. (**b**) There are scattered Civatte bodies. Overall, the case is compatible with lichenoid esophagitis pattern. Review of the patient history revealed that it may be associated with hepatitis B infection

- Clinical correlation is required to arrive at a diagnosis

Case History

A 26-year-old female with epigastric pain and history Crohn disease.

Endoscopic Finding

Mild esophageal erythema.

Differential Diagnosis Prior to Slide Review

- Upper tract involvement of Crohn disease
- Medication effect
- Lymphocytic esophagitis
- GERD
- EoE

Histologic Findings

Squamous mucosa with reactive epithelial changes (elongated papillae, mild basal layer hyperplasia) and areas with scattered intraepithelial eosinophils (Fig. 2.14a) and other areas with scattered intraepithelial lymphocytes (Fig. 2.14b).

Differential Diagnosis After Slide Review

- Upper tract involvement of Crohn disease

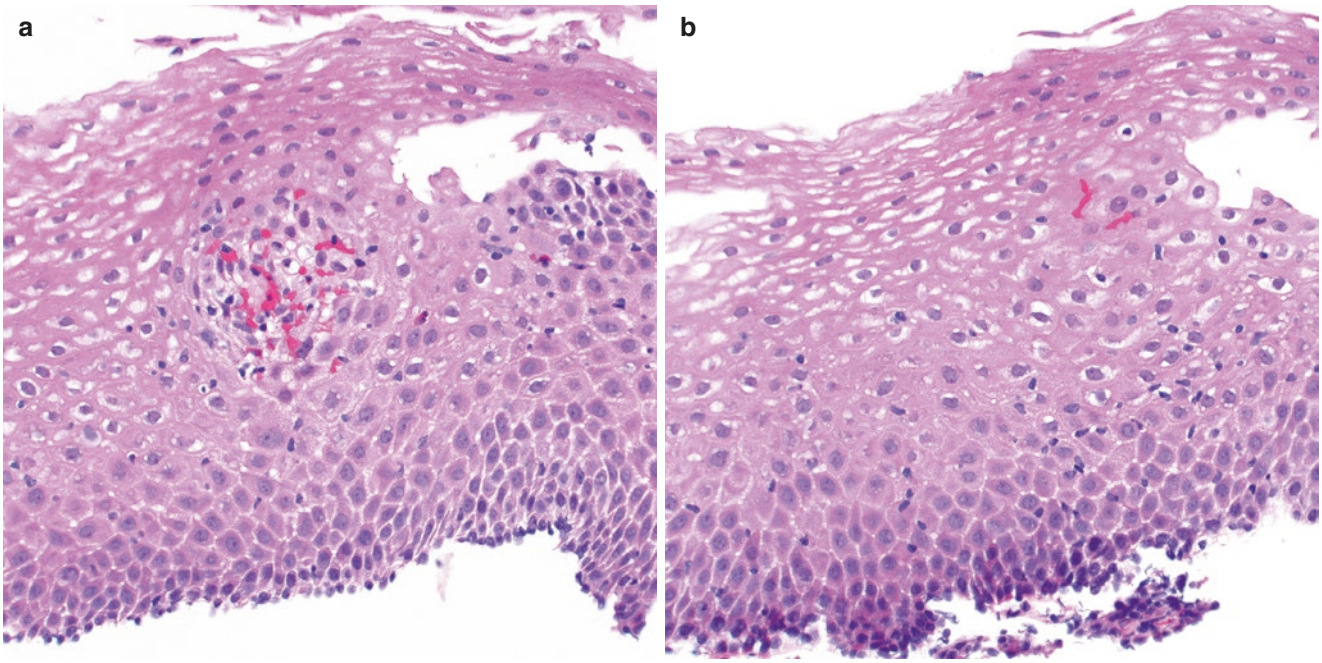

Fig. 2.14 Case 3. Squamous mucosa with mild reactive epithelial changes and scattered intraepithelial (**a**) eosinophils and (**b**) lymphocytes in a patient with a history of Crohn disease

- Medication effect
- Lymphocytic esophagitis
- GERD

IHC and Other Ancillary Studies
None.

Final Diagnosis
Squamous mucosa with reactive epithelial changes and scattered intraepithelial eosinophils and lymphocytes.

- Given the clinical history, these findings could represent upper tract involvement of Crohn disease, but medication effect and reflux esophagitis cannot be entirely excluded.

Take-Home Messages
- In addition to reflux esophagitis and eosinophilic esophagitis, Crohn disease, medication effect, and collagen vascular disease can have intraepithelial eosinophils.
- Often clinical correlation is necessary to arrive at the optimal diagnosis and treatment plan.

Case 4

Learning Objectives
- Bullous disease of the esophagus can be difficult to diagnose, but the clinical features, level of split, and DIF can aid in the diagnosis

Case History
A 42-year-old female with odynophagia. Bullae, blisters, and erosions of the oral mucosa.

Endoscopic Finding
Sheets of sloughed mucosa and erosions on withdrawal of the endoscope.

Differential Diagnosis Prior to Slide Review
- Pemphigus vulgaris
- Esophagitis dissecans superficialis (sloughing esophagitis)
- Bullous pemphigoid
- Epidermolysis bullosa
- Herpes esophagitis
- CMV esophagitis
- *Candida* esophagitis

Histologic Findings
Suprabasal split of the squamous mucosa with acantholytic cells (Fig. 2.15a). Detached squamous epithelium shows loss basal layer, elongated papillae, and intercellular edema with little inflammation (Fig. 2.15b). Lamina propria with irregular papillae and clinging basal layer of epithelium with the so-called "tombstone" appearance (Fig. 2.15c).

Differential Diagnosis After Slide Review
- Pemphigus vulgaris
- Bullous pemphigoid
- Epidermolysis bullosa

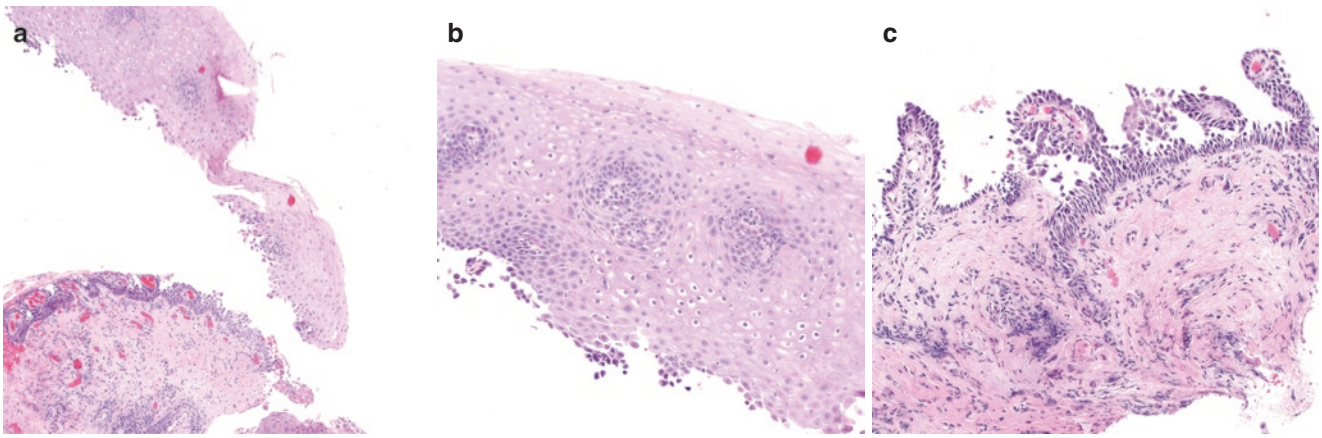

Fig. 2.15 Case 4. (**a**) Suprabasal splitting of the squamous epithelium with scattered acantholytic cells. (**b**) The detached squamous epithelium shows mild reactive epithelial changes with little inflammation. (**c**) The lamina propria with papillae highlights a clinging basal layer in the typical "tombstone" pattern of pemphigus vulgaris

- Herpes esophagitis
- Esophagitis dissecans

IHC and Other Ancillary Studies

- DIF shows intercellular IgG and C3.
- Indirect immunofluorescence is positive for PV antibodies.

Final Diagnosis

Pemphigus vulgaris.

Take-Home Messages

- Pemphigus vulgaris is a bullous disease that often affects the esophagus.
- It is characterized histologically by a suprabasal split with a tombstone appearance of the basal layer clinging to the lamina propria.
- DIF can aid in differentiating bullous diseases.

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