Several non-neoplastic entities involving the esophagus and the stomach have been recently highlighted in the medical literature. Some of these entities are newly recognized and are often underdiagnosed because of insufficient awareness. Furthermore, much of the etiology, pathogenesis, natural history, treatment, and patient outcomes remain unknown or only partially defined. The objective of this review is to increase familiarity with these entities among gastroenterologists and pathologists alike with the goal of promoting detection and increased reporting of cases and ultimately improving our understanding of these entities.

ESOPHAGITIS DISSECANS SUPERFICIALIS OR SLOUGHING ESOPHAGITIS

Some authors consider esophagitis dissecans superficialis (EDS) and sloughing esophagitis (SE) as 2 different entities with overlapping endoscopic and histopathologic features, whereas others consider them as 1 disease. They are discussed together in this review because of the shared characteristic endoscopic findings of SE mucosa.

EDS/SE is a rare benign condition; there are fewer than 200 cases reported in the English medical literature. It affects the superficial layers of the squamous lining of the esophagus. Early reports of EDS had rather dramatic descriptions including vomiting of the esophageal epithelium in the form of a “tubular cast.” In most cases of EDS/SE, however, the endoscopic findings are not as dramatic and range from white patches of peeling esophageal epithelium affecting the mid to distal esophagus to diffuse sloughing of the entire esophageal epithelium (Fig. 1). Involvement limited to the proximal esophagus has only been reported in a few cases. One study described the esophageal endoscopic impression of EDS as “filled with gift-wrap paper.” The mucosa underneath the peeled “membrane” is often unremarkable (Figs. 1A and 1D). Additional esophageal findings during endoscopy are infrequent and may include erythema, ulceration, mucosal nodularity, rings, and even strictures.

The most characteristic histopathologic feature of EDS/SE is a “mummified” superficial squamous epithelium and an unaltered basal layer; this gives a 2-toned appearance at low magnification (Fig. 2). Squamous cells in the superficial layers are necrotic (coagulative necrosis) and thus have pyknotic to faded (ghost) nuclei and intense eosinophilic cytoplasm on routine hematoxylin and eosin stain. The eosinophilic top layer of the squamous mucosa is often separated from the underlying intact squamous mucosa, and this sometimes creates a blister-like appearance (Figs. 2A and 2C). Inflammation is rarely seen and, if present, is often seen at the junction between the necrotic epithelium and the underlying normal squamous mucosa.

EDS/SE affects patients between the third and the eighth decades of life (range 14-90) with probable equal distribution between the sexes; only a few cases have been reported in pediatric patients. EDS/SE often presents with nonspecific clinical symptoms (eg, cough, dysphagia, globus sensation, regurgitation, chest or epigastric pain, heartburn, nausea and vomiting), and the diagnosis is often not suspected until endoscopic examination.

The etiology remains unknown, but EDS/SE is frequently associated with chemical trauma to the esophageal mucosa caused by polypharmacy, especially central nervous system depressants, nonsteroidal anti-inflammatory drugs, and bisphosphonates. In addition, this condition has been associated with thermal and physical trauma to the esophageal mucosa including ingestion of hot beverages and very rarely sclerotherapy for esophageal varices. Other reported rare associations include bullous skin diseases such as bullous pemphigoid and pemphigus vulgaris, celiac disease, and heavy smoking. Distinguishing EDS/SE from esophageal manifestations of bullous skin diseases can be challenging on clinical grounds, but their histologic and immunofluorescence patterns differ.

In the study by Purdy et al, SE was encountered in patients affected by debilitating conditions such as being...
bedridden, and being immunosuppressed for transplantation. These patients did not receive treatment, and all had poor overall clinical outcomes as a result of their underlying diseases.1 In contrast, most other studies in the medical literature with follow-up information reported improvements and often complete resolution after discontinuation of the precipitating medications and treatment with proton pump inhibitors and/or corticosteroids.2,5

ESOPHAGEAL LEUKOPLAKIA OR ESOPHAGEAL EPIDERMOID METAPLASIA

Leukoplakia is a clinical term used to describe a persistent white patch or plaque encountered on the mucous membrane. Leukoplakia of the esophagus or esophageal epidermoid metaplasia is a rare condition reported in the medical literature only in case reports and a few small case series.15-20 Only 6 cases were observed in a study of 1000 autopsies,21 and none was encountered among 198 consecutive esophageal biopsies over a 6-month period at 3 academic institutions in the United States.19

The characteristic endoscopic features of leukoplakia of the esophagus or esophageal epidermoid metaplasia include a slightly elevated lesion, clear demarcation from the surrounding uninvolved tissue, a translucent white color, and a shaggy or cobblestone surface (Fig. 3).15,17,19 The distal third of the esophagus is most often affected.

The endoscopic differential diagnosis includes glycogenic acanthosis, esophageal papilloma, plaques associated with reflux, infections such as *Candida* esophagitis, and superficial esophageal cancer.15,16,22 The key feature to distinguish this entity from inflammatory lesions is its clear border.15 Lugol’s iodine stain may be helpful to distinguish epidermoid metaplasia from papilloma and esophageal glycogenic acanthosis. The former has no staining, whereas the latter 2 show weak (squamous papilloma) to strong staining (glycogenic acanthosis).15,16,18 In terms of superficial carcinomas, they tend to be multiple and tinged with pink color over time on Lugol’s iodine stain. Readers are referred to the study by Ezoe et al15 for additional criteria for distinguishing epidermoid metaplasia from other plaque-like lesions during endoscopic examination. Needless to say, esophageal biopsy also greatly facilitates the diagnosis of the lesion.

Although sharing the same endoscopic findings, esophageal leukoplakia and esophageal epidermoid metaplasia have slightly different histopathologic features. We believe that they are within the same spectrum of changes that one can appreciate in epidermal hyperplasia. In fact, we provide the 2 diagnostic terms together as “esophageal leukoplakia/esophageal epidermoid metaplasia” in our daily pathology practice. The characteristic histopathologic features of esophageal leukoplakia include hyperplasia, acanthosis, and parakeratosis of the superficial layers of esophageal squamous mucosa. Sometimes these are
accompanied by pronounced basal hyperplasia and/or a sharply demarcated midzone with vacuolated cells and, sometimes, scatter neutrophils. The key histopathologic finding in esophageal epidermoid metaplasia is a prominent granular layer accompanied by an overlying compact hyperorthokeratotic layer (Fig. 4). This feature is very similar to and even can be indistinguishable from the skin; hence the terminology. Additional features of epidermoid metaplasia include sharp demarcation from surrounding normal esophageal mucosa (Fig. 4A), flattening of the rete pegs, a thickened basal layer, and moderate acanthosis of the midzone. The term orthokeratotic dysplasia has been used for essentially identical lesions of the oral mucosa by Japanese colleagues. The etiology is not clear, but chronic irritation caused by esophageal stenosis and dysmotility has been suggested as the inciting factor. Unlike oral leukoplakia, which is considered a potentially malignant disorder by the World Health Organization, the malignant potential of esophageal leukoplakia or esophageal epidermoid metaplasia has not been extensively studied and thus is not clear. This is in part attributable to the rarity of the condition and the lack of reported cases in the literature. A recent study by Singhi et al showed persistent disease in 54% of patients (7/13) with esophageal epidermoid metaplasia, and one progressed to dysplasia or carcinoma within a mean follow-up period of 2.3 years (range 2–8.3 years).

On the other hand, this study, together with other studies, suggests an association between leukoplakia of the esophagus or esophageal epidermoid metaplasia and adjacent high-grade squamous dysplasia and/or squamous cell carcinoma. Because of this association, although data remain limited, we suggest that our gastroenterology colleagues initiate a surveillance program for patients with a diagnosis of esophageal leukoplakia or esophageal epidermoid metaplasia in our pathology practice.

**ESOPHAGEAL LICHEN PLANUS AND LICHENOID ESOPHAGITIS**

Lichen planus (LP) is an idiopathic papulosquamous eruption involving the skin, nails, and mucosal surfaces. Cutaneous LP has a prevalence as high as 1% worldwide and affects predominantly middle-aged adults without sex predilection. In contrast, LP of mucosal surfaces is predominantly a disease of middle-aged women. It can include lesions of the oral mucosa, pharynx, and perineum but most commonly affects the oral mucosa. In fact, oral involvement may coexist with cutaneous LP in 30% to 50% of LP patients and 25% of patients affected by LP present with oral lesions alone. Although as many as 7% of oral LP patients may have spontaneous remission, 1.2% to 2.3% of patients with oral LP may progress to malignancy,
namely, squamous cell dysplasia and squamous cell carcinoma. Neither remission nor malignant transformation is related to the duration of disease.29,30

Similar to oral LP, esophageal LP affects mainly middle-aged women and often coexists with cutaneous and mucosal LP.31-35 In the study by Katzka et al,35 esophageal LP was the sole manifestation of LP in 2 of 27 patients, and the esophagus was the initial presenting site in 13 of the 27 patients. In contrast to cutaneous and oral LP, esophageal LP remains underdiagnosed, and therefore the prevalence is unknown. This is partly because many patients remain asymptomatic or experience only minor nonspecific esophageal symptoms, predominantly dysphagia, until their disease progresses to esophageal stricture. In a recent study by Quispel et al,33 50% (12 of 24) of patients with oral and/or cutaneous LP had esophageal LP detected by magnification chromoendoscopy and further proven by histopathologic evaluation. For the same reason, the risk of malignancy is also not well established, but a small number of cases associated with malignant transformation to esophageal squamous dysplasia, squamous cell carcinoma, and verrucous carcinoma have been reported.32,34-37

Esophageal LP most often affects the upper and middle thirds of the esophagus.32,35 The characteristic endoscopic features of esophageal LP include mucosal sloughing, friability on contact, hyperemia, and ulceration (Fig. 5).32,33,35 Whitish papules are often seen in esophageal LP, but this finding is nonspecific.35 In advanced disease, esophageal strictures may form, mainly in the proximal esophagus but also elsewhere in the esophagus.35

The characteristic histologic features include a prominent bandlike infiltrate of lymphocytes involving the epithelium and lamina propria, damage of the basal layer of the epithelium and scattered degenerated keratinocytes termed Civatte bodies (Figs. 6A, C, and D).31 The presence of bandlike lymphocytosis alone is not diagnostic of esophageal LP. Other conditions associated with esophageal intraepithelial lymphocytosis include medication-associated injury, reactive changes associated with ulcer, and GERD.38 Clinicopathologic and endoscopic-pathologic correlation is often required to establish a diagnosis of esophageal LP. Direct immunofluorescence (DIF) studies have proved useful.

A recently described pattern of esophageal injury, called lichenoid esophagitis, has clinical and histopathologic features nearly identical to those of established esophageal LP.34 Patients descriptively diagnosed with lichenoid esophagitis do not have positive DIF, but their esophageal biopsy specimens demonstrate histopathologic features indistinguishable from those seen in esophageal LP (Figs. 6B-D). Lichenoid esophagitis is associated with HIV infection and viral hepatitis including hepatitis B and hepatitis C; this association with viral infections has not been reported in esophageal LP. On the other hand, both esophageal LP and lichenoid esophagitis are associated with polypharmacy, rheumatologic diseases, and esophageal strictures; both may progress to malignancy.34

**AUTOIMMUNE METAPLASTIC ATROPHIC GASTRITIS AND ATROPHIC AUTOIMMUNE PANGASTRITIS**

Autoimmune metaplastic atrophic gastritis (AMAG), although not a newly recognized disease, often causes confusion and delay in diagnosis, which subjects patients to increased risk of the development of pernicious anemia and other the sequelae of AMAG.

AMAG is a chronic gastric inflammatory disease caused by parietal cell antibodies to the gastric proton pump, the H/K ATPase.39 AMAG affects the gastric body and fundus where the parietal cell-containing oxyntic glands reside, and thus it is different from the antral gastritis typically associated with *H pylori* infection. In patients affected by AMAG, intrinsic factor antibodies and ultimately pernicious anemia may develop as a result of vitamin B12 deficiency. Destruction of parietal cells results in hypergastrinemia and subsequently enterochromaffin-like (ECL) cell hyperplasia in the gastric body and fundus. Thus, patients with AMAG also have increased risk of the development of neuroendocrine neoplasms and gastric cancer.40,41

The precise prevalence of AMAG remains unknown because it is often underdiagnosed in its early stage when many patients do not have vitamin B12 deficiency and the
histopathologic features are not fully developed. Once considered a disease that preferentially affects elderly women of Northern European descent, current data suggest that (1) AMAG occurs at a similar frequency across all racial groups, (2) women are preferentially affected, (3) the reported overall prevalence is as high as 2.7% in women and 1.4% in men, and (4) a higher prevalence, as high as 4.3%, and earlier age at onset are seen in nonwhite women when compared with white women.39,42,43

The histopathologic features, endoscopic findings, and clinical presentations of AMAG evolve over time. The histopathologic features of early AMAG are subtle and can be challenging when the stomach is not well sampled or the pathologist is not familiar with early manifestations of AMAG. The constellation of histopathologic findings supporting a diagnosis of early AMAG includes multifocal or diffuse lymphoplasmacytic infiltration in the deep portion of the lamina propria, ie, a “bottom-heavy” inflammatory infiltrate, scattered destruction of individual oxyntic glands by lymphocytes, parietal cell pseudohypertrophy, ECL cell hyperplasia, and various types of metaplasia (Fig. 7).39,44,45

The latter 3 features may not present in all cases of early AMAG. In the study by Torbenson et al,45 22 of 34 cases (65%) of early AMAG in patients without proton pump inhibitor treatment at the time of biopsy showed parietal cell pseudohypertrophy reminiscent of the effect in parietal cells induced by proton pump inhibitors, and 11 cases of early AMAG with positive serologic anti-intrinsic factor antibody or antiparietal cell antibody showed at least linear ECL cell hyperplasia on chromogranin A immunostaining. Also reported in this study were 65% of cases (22/34) with intestinal (16/34; 47%), pyloric (16/34; 47%), and even pancreatic acinar cell (2/34; 6%) metaplasia.45 Pancreatic acinar cell metaplasia, if present in gastric biopsy specimens taken from oxyntic mucosa, may be a strong indicator for AMAG because it is much more frequently found in gastric biopsy specimens with AMAG than specimens with other types of gastritis or in biopsy specimens of normal oxyntic mucosa.46

The main histopathologic differential diagnosis for early AMAG is *H pylori* gastritis involving the oxyntic mucosa. Helpful features to distinguish them include the distribution and nature of the inflammatory infiltrate, the distribution of metaplasia, identification of organisms, and ECL cell hyperplasia.47 In addition, a subset of patients affected by early AMAG may have coexisting *H pylori* infection.44,45
Of interest, some authors have proposed that *H pylori* infection may cause AMAG in susceptible individuals by inducing autoantibodies to parietal cell through molecular mimicry.47,48

Fully established AMAG presents with a profound loss of the parietal cell mass and thus atrophy of oxyntic glands. This finding together with deep, dense, diffuse lymphoplasmacytic infiltration and metaplasia of the intestinal, pyloric, and pancreatic types are characteristic of AMAG (Figs. 8A, C, and E). Nodular ECL cell hyperplasia can be highlighted by chromogranin A immunostaining (Fig. 8E). Late-stage AMAG is characterized by complete atrophy of oxyntic mucosa with minimal inflammation, and the affected gastric mucosa often has an empty appearance. Metaplasia is widespread, and ECL cell hyperplasia is almost always present.39 Compared with the often strikingly atrophic and inflamed oxyntic mucosa, the antral mucosa is rather unremarkable in the absence of current or past *H pylori* infection; there may be reactive changes and foveolar hyperplasia but no atrophy, metaplasia, or ECL cell hyperplasia (Figs. 8B, 8D, and 8F).39,49

Patients affected by AMAG have an increased risk of the development of non-neoplastic lesions including oxyntic gland “pseudopolyps” and hyperplastic polyps, as well as neoplastic lesions including intestinal and pyloric gland adenomas, well-differentiated neuroendocrine (carcinoid) tumors, and gastric adenocarcinoma. Awareness of this association is of critical importance for gastroenterologists when performing endoscopic evaluation of the gastric mucosa of patients with gastric lesions.

In the early phases of AMAG, the body and fundus of the stomach may not have any endoscopically recognizable changes or may just have nonspecific atrophy with mucosal thinning and loss of rugal folds (Fig. 9A). In this background of incomplete atrophy, the islands of relatively preserved, normal oxyntic glands may appear as polyps endoscopically (Fig. 9B).43,50-53 In the study by Park et al,43 20 pseudopolyps were detected in 143 AMAG patients with gastric lesions. Furthermore, in the study by Krasinskas et al50 pseudopolyps were found in the body and fundus and are often multiple.

Patients with AMAG may also have true polyps arising in the gastric mucosa; these include hyperplastic polyps, intestinal-type gastric adenoma, pyloric gland adenoma, and well-differentiated neuroendocrine (carcinoid) tumors presenting endoscopically as polypoid lesions. Hyperplastic polyps are the most common type of gastric polyps in AMAG patients; 138 hyperplastic polyps were detected in 143 AMAG patients with gastric lesions in the study by Park et al.53 Although many of these patients have multiple hyperplastic polyps,49 a subset of AMAG patients do present with antrum-restricted hyperplastic polyps (6/16; 38% in the study by Abraham et al49).

Figure 6. Histopathologic features of esophageal lichen planus (A) and lichenoid esophagitis (B) are identical and include a bandlike infiltrate of lymphocytes involving the epithelium and lamina propria. The basal layer is damaged (C), and there are scattered Civatte bodies (A, B, and D, arrows). B: Photomicrograph was taken from esophageal biopsy specimens of a patient who had HIV infection (well controlled) and hepatitis C viral infection. A, B, original magnification, ×200; C and D, original magnification, ×400; all photomicrographs are from hematoxylin and eosin–stained tissue sections.
Additionally noted in the study by Park et al were 18 intestinal-type gastric adenomas, 3 pyloric gland adenomas, 46 well-differentiated neuroendocrine (carcinoid) tumors, 1 GI stromal tumor, 3 lymphomas (2 mucosa-associated lymphoid tissue type of extranodal marginal zone lymphoma, and 1 large B-cell lymphoma arising in gastric mucosa without *H. pylori* infection), and 11 adenocarcinomas in the 143 AMAG patients with gastric lesions. Intestinal-type gastric adenoma, although not as frequently associated with AMAG as hyperplastic polyps, is a precursor lesion. The well-differentiated neuroendocrine (carcinoid) tumors associated with AMAG are usually small, often multiple, arise in a background of ECL cell hyperplasia, and have negligible metastatic potential.

In patients who present with gastric polyps or polypoid lesions, biopsy of the lesion or polypectomy alone may not be diagnostic of the underlying gastric disease. Sampling various locations of the flat mucosa from both the body/fundus and the antrum away from the gastric polyps during endoscopic examination is of great importance in identifying the underlying gastric pathology.

Last, pernicious anemia, the well-known outcome of the late-stage AMAG, takes decades to develop. As demonstrated in the study by Hershko et al, 83 of 160 patients with autoimmune gastritis identified by hypergastrinemia and positive antiparietal cell antibodies presented with iron deficiency anemia, 48 patients with normocytic anemia, and only 29 patients with macrocytic anemia. When stratified by ages from younger than 20 years to older than 60 years, the mean corpuscular volume and serum concentration of gastrin progressively increased, whereas serum concentration of cobalamin (vitamin B12) progressively decreased among their cohorts. Iron deficiency in AMAG patients is a result of achlorhydria. This is because gastric acidity is required to render dietary iron soluble. The decrease in gastric acidity caused by the reduction in gastric acid produced by parietal cells leads to reduced iron absorption and thus iron deficiency anemia. By the same token, these patients are likely to be refractory to oral iron supplement therapy. As such, a high index of suspicion for AMAG is necessary when evaluating a patient with refractory iron deficiency anemia without clear etiology. The initial evaluation in the setting of suspected AMAG should also include serum gastrin concentration and antiparietal cell antibodies.

The main differential diagnosis for AMAG is the environmental atrophic gastritis associated with long-standing...
H pylori infection, as discussed previously. A third type of atrophic gastritis described in 2006 is atrophic autoimmune pangastritis. This entity should be included in the differential diagnosis for AMAG. The characteristic histologic features of atrophic autoimmune pangastritis are as follows. There is intense, “bottom-heavy” lymphoplasmacytic and neutrophilic inflammation that persists even when the mucosa has complete atrophy (Fig. 10). This is different from both the inflammation in AMAG, which tends to diminish in advanced atrophy, and the superficial inflammation in H pylori gastritis. The disease process involves both the antrum and body, and there is no ECL cell hyperplasia or H pylori infection. In the study by Jevremovic et al., all 8 patients affected by atrophic autoimmune pangastritis had systemic autoimmune diseases and/or connective tissue diseases, such as autoimmune enterocolitis and disabling fibromyalgia, with positive serum autoimmune markers in 7 of 8 patients. However, the status of antiparietal cell and anti-intrinsic factor antibodies was mostly unknown in these patients. On the other hand, 4 of the 8 patients had antigoblet cell and antienterocyte antibodies. An autoimmune process targeting multiple gastric cell lineages was proposed. In addition, atrophic autoimmune pangastritis may be associated with increased risk in gastric cancer because 1 of 8 patients presented with multifocal persistent low-grade dysplasia. Patients may improve after immunosuppressive therapy.
SUMMARY

The definitive diagnosis of these entities requires a high index of suspicion and correlation among clinical, endoscopic, and pathologic findings. Much about many aspects of these diseases remains unknown. Awareness of these entities and their clinical significance may allow improved recognition and patient care.

REFERENCES

1. Purdy JK, Appelman HD, McKenna BJ. Sloughing esophagitis is associated with chronic debilitation and medications that injure the esophageal mucosa. Mod Pathol 2012;25:767-75.


1. The most common type of gastric polyp seen in atrophic autoimmune gastritis is
   a. hyperplastic
   b. carcinoid
   c. gastric type adenomas
   d. intestinal type adenomas

2. Characteristics of esophageal leukoplakia include
   a. also known as esophageal epidermoid metaplasia
   b. on endoscopy, it appears as a yellow polypoid lesion
   c. no staining with Lugol’s iodine solution
   d. on histology, a prominent granular layer with an overlying hyperorthokeratotic layer is characteristic.

3. Esophageal lichen planus
   a. most often involves the upper or middle third of the esophagus
   b. most often affects middle age men who smoke
   c. endoscopically it appears as a white plaque
   d. is associated with HIV and HCV infection

True or False

4. Sloughing esophagitis may be a manifestation of medication-induced esophageal injury

5. Leukoplakia of the esophagus, although not premalignant, may be associated with adjacent squamous cell carcinoma

6. Esophagitis dissecans superficialis is associated with an increased risk of esophageal perforation

7. Patients with pernicious anemia are likely to present first with iron deficiency anemia before developing B12 deficiency.

8. The presence of enterochromaffin cell hyperplasia is typical for autoimmune atrophic gastritis

9. Iron deficiency anemia as a result of atrophic autoimmune gastritis is easily corrected with oral iron supplements

10. Autoimmune atrophic gastritis is characterized by antibodies directed against the gastrin receptor in the parietal cell

11. When gastric polyps are identified, the surrounding mucosa should be biopsied to exclude autoimmune gastritis