REVIEW

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Major variants of esophagitis

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The term esophagitis refers to any inflammatory condition that affects the esophageal mucosa or wall. There is a wide variety of causes leading to esophageal inflammation, including reflux disease, infections (e.g. herpes simplex or *Candida albicans*), drugs, exposure to physical or chemical agents (e.g. radiotherapy or corrosives), and systemic inflammatory/immune disorders (e.g. Crohn's disease, collagen vascular disease) (1). However, esophagitis of these various etiologies often presents with overlapping histologic features such as epithelial hyperplasia, intraepithelial edema, and inflammatory cell infiltration comprising neutrophils, lymphocytes and eosinophils within the squamous epithelium, all representing reactive changes to injury (2,3). Therefore, correlating the clinical, endoscopic and histologic findings is crucial in arriving at the correct diagnosis. In this review, the clinicopathologic features of the major types of esophagitis are summarized.

Reflux esophagitis (RE)

RE is defined as the inflammation of the lower esophagus due to damage caused by acid reflux resulting from lower esophageal sphincter dysfunction (1). RE occurs at all ages and in both sexes, though there is a slight male predominance. Clinically, RE may present as nonerosive reflux disease (NERD) including patients with normal endoscopy with or without positive pH monitoring, as erosive reflux disease (ERD) including patients with positive endoscopy, or as complicated RE comprising ulcers, strictures, hemorrhage, Barrett's esophagus, and adenocarcinoma (4,5). Typical symptoms are heartburn and regurgitation occurring more frequently after a fatty meal (6). Epigastric pain, chronic hoarseness and protracted hiccups are less frequently observed, while there is a large group of asymptomatic patients (6,10). RE is a multifactorial disorder, with different abnormalities predominating in different patients. Predisposing factors include i) decreased esophageal sphincter pressure, ii) diminished esophageal clearance resulting from defective peristalsis, iii) delayed gastric emptying or abnormal gastric contractility, iv) decreased salivary flow, and v) increased gastric acid production (1,2). Esophageal dysmotility contributes to decreased clearance of the refluxed material, thereby leading to an increased mucosal contact time. The composition and length of time of mucosal contact of the reflux material determine the severity of the disease (1,6). RE involves the most distal part of the esophagus, and the gastroesophageal junction in particular. Even though most patients with RE have classic endoscopic findings of erythema, mucosal edema, erosions, or ulcers, many patients with typical reflux symptoms have normal or nearly normal endoscopy (i.e. NERD) (6). In contrast to RE, eosinophilic esophagitis (EoE) involves not only the distal esophagus; the mid and upper esophagus are also frequently involved (7). RE is associated with a variety of histologic features, representing changes from secondary to acid injury and mucosal healing (2,5). Histopathologic features of acid reflux are nonspecific and include epithelial hyperplasia, balloon cells, basal cell hyperplasia, papillary elongation, vascular congestion, inflammatory cell infiltration comprising lymphocytes, neutrophils and eosinophils, and dilated intercellular spaces (DIS) representing epithelial edema (3,8). Several investigators have developed grading schemes for each of these histologic criteria in an attempt to correlate with disease severity and also to aid in the differential diagnosis (7,9,10).

Eosinophilic esophagitis (EoE)

EoE is a chronic inflammatory disorder characterized by eosinophilic infiltration of the esophageal mucosa associated with a history of atopy or allergy (9). EoE was first described in a case report in 1978 by Landres et al. (11). Attwood and colleagues (12) subsequently presented the first detailed study of EoE in 1993, describing intense eosinophilic infiltration in the esophageal mucosa of 12 patients presenting with severe dysphagia and absence of acid reflux. Eosinophil infiltration of the esophageal mucosa is the cardinal pathologic feature, although it may occur secondary to several unrelated diseases such as eosinophilic gastroenteritis, hypereosinophilic syndrome, drug exposure, parasitic and fungal infections, RE, esophageal leiomyomatosis, and scleroderma (7,13,14). EoE shows an age predilection of children and young adults, with a male predominance (9,13). Progressive dysphagia typically described as intermittent and mostly induced with solid foods (15) and food impaction are the most common presenting symptoms in adult patients with EoE (13,16),

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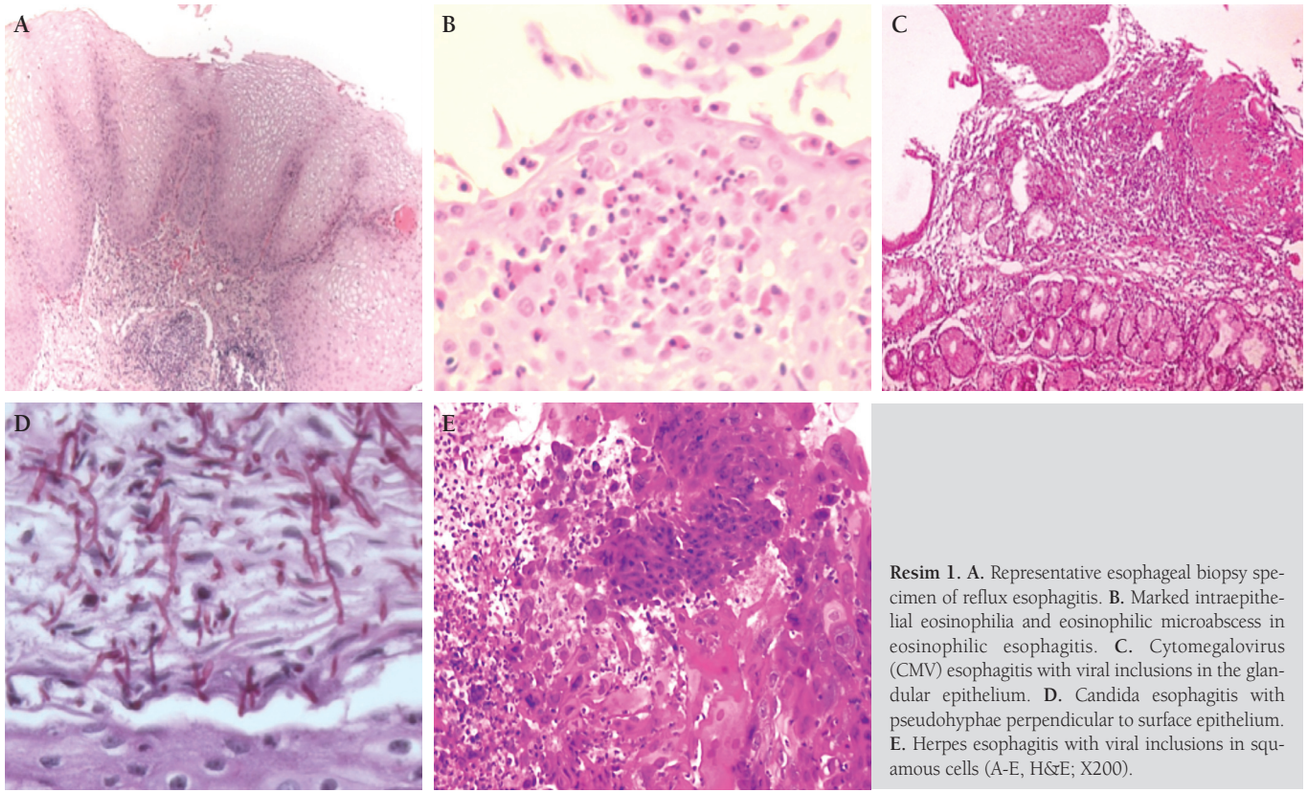
while children typically present with feeding refusal, food intolerance, vomiting, abdominal pain, and failure to thrive (15,17). EoE involves not only the distal esophagus; the mid and upper esophagus are also frequently involved. Despite the lack of a pathognomonic endoscopic sign for EoE, red furrows, white exudates, "crepe paper" mucosa (i.e. fragile mucosa), corrugated rings, and severe stenosis are the most characteristic endoscopic findings (15,18). They seem to be related to the architectural changes resulting from chronic inflammation leading to fibrosis (15). In contrast to reflux disease, patients with EoE have normal pH monitoring and usually do not respond to acid suppression (12,16). According to the criteria of FIGERS (First International Gastrointestinal Eosinophil Research Symposium), the diagnosis of EoE relies upon clinical and histological exclusion of RE and other causes of mucosal eosinophilia (19). Therefore, ambulatory pH monitoring, endoscopy and biopsy appear to be the most valuable procedures for the diagnosis of EoE (15,18).

A different pathogenetic mechanism is involved in EoE, which seems to be linked to allergic responses to food or airborne allergens, but cases have also been reported in which patients have EoE without detectable food allergies by patch or prick skin testing (14,20). This indicates that EoE could also be associated with immune dysregulation, and these tests might not reflect hypersensitivity driven by discrete antigens (20). The mechanism is believed to be mediated through activation of Th2 lymphocytes leading to an increased production of proallergenic interleukins (IL), especially IL-4, IL-5 and IL-13. While IL-5 promotes maturation of eosinophils and migration from the bone marrow into the circulating blood stream, IL-4 and IL-13 upregulate the production of eotaxin 3 by the epithelium, a chemokine responsible for attracting the eosinophils into the esophagus (13). As a result, mature eosinophils accumulate in the esophagus, are activated and degranulate, releasing multiple cytotoxic agents. Though the mechanism of fibrogenesis is still unclear, IL-5, by inducing fibroblast-myofibroblast transdifferentiation, may be the critical molecule for tissue fibrosis as well as smooth muscle hyperplasia that leads to esophageal stricture formation in EoE (14).

In EoE, biopsies show marked eosinophilic infiltrate at different levels of the esophagus. However, the presence of an increased number of eosinophils in the esophageal squamous epithelium is a nonspecific finding that may be seen in several disorders, including RE, infections, drugs, and Crohn's disease (9,14). In order to distinguish EoE from other causes of mucosal eosinophilia, major and minor histologic criteria for the diagnosis of EoE have been described (18). Major features include epithelial eosinophilia >15 eosinophils/high-power field (hpf) and "microabscesses", described as clustering of 4 or more eosinophils and superficial layering of eosinophils. Minor criteria include basal cell hyperplasia, papillary elongation, spongiosis (intercellular edema), which is currently known as DIS, and inflammatory cell infiltration (14,18,26).



Resim 1. A. Representative esophageal biopsy specimen of reflux esophagitis. **B.** Marked intraepithelial eosinophilia and eosinophilic microabscess in eosinophilic esophagitis. **C.** Cytomegalovirus (CMV) esophagitis with viral inclusions in the glandular epithelium. **D.** Candida esophagitis with pseudohyphae perpendicular to surface epithelium. **E.** Herpes esophagitis with viral inclusions in squamous cells (A-E, H&E; X200).

Infectious esophagitis

Infection is an important cause of esophagitis, especially in immunocompromised hosts. It can occur under various clinical settings including gastroesophageal reflux disease (GERD), advanced age, immunodeficiency states, chronic alcoholism, diabetes, and motility disorders (2). *C. albicans,* cytomegalovirus (CMV), and herpes simplex virus (HSV) are the most frequently observed causative agents of infectious esophagitis (1,2).

Bacterial esophagitis

The presence of bacteria within esophageal specimens does not always imply the presence of an infection. Organisms can be swallowed or carried into the esophagus by the endoscope. Bacteria lying freely on the surface or in the lumen are unlikely to be pathogens. Mostly, bacteria are found in biopsies from patients with CMV, HSV, or Candida esophagitis (1). Bacterial esophagitis, on the other hand, is defined as the presence of bacterial invasion of the esophageal epithelium or deeper layers with no concomitant fungal or viral infection (1,2). It usually involves the previously damaged mucosa, by GERD, radiation, chemotherapy, or nasogastric intubation (1,21). The commonest causes of bacterial esophagitis include *Staphylococcus aureus*, epidermidis, and Streptococcus strains (21). Bacterial esophagitis presents with odynophagia, dysphagia, chest pain, or upper gastrointestinal bleeding. The most significant complications are perforation, fistulas and sepsis; the risk correlates with the severity of esophagitis. Bacteria can be found on Gram-stained sections in the vicinity of ulcers and erosions (22).

Viral esophagitis

Viral esophagitis is very common, particularly in immunocompromised hosts. This includes HSV, CMV, Epstein-Barr virus (EBV), and human papilloma virus (HPV) (1).

Herpes esophagitis

Herpes esophagitis is primarily a disease of immunocompromised patients with solid organ or bone marrow transplants (23). Herpes esophagitis can be caused by either HSV type 1 or type 2. Primary infection is common in neonates with disseminated HSV, while in adults most cases represent reactivation of latent HSV type (24). Patients typically present with acute- onset nausea and vomiting, fever, odynophagia, dysphagia, and chest pain (15,24). Oral herpetic blisters may suggest the diagnosis, though they are found in only one-fourth of the patients (23). Endoscopically, multiple vesicles, erosions and ulcers with an exudate can be seen (23). Histologically, characteristic lesions include the presence of multinucleated giant cells and intranuclear inclusions within the squamous epithelium (24). There are two types of herpetic intranuclear inclusions: large basophilic inclusions that fill the entire nucleus – Cowdry type B, and small eosinophilic inclusions with a clear halo around them – Cowdry type A. Inclusions are usually found at later stages of the disease and are located at the edge of an ulcer (24). When viral inclusions are absent due to sampling error, presence of mononuclear cell infiltrate including macrophages with convoluted nuclei adjacent to the infected epithelium is a helpful diagnostic feature. Immunohistochemistry (IHC) may be useful but is rarely necessary (24).

Cytomegalovirus (CMV) esophagitis

Immunocompromised hosts, particularly acquired immunodeficiency syndrome (AIDS) patients and transplant recipients, are at high risk for CMV esophagitis, which is usually accompanied by systemic CMV infection (23). Patients with disseminated CMV infection have circulating cytomegalic inclusion-containing endothelial cells in their peripheral blood. Though clinical findings are similar to herpes esophagitis, endoscopically, a single ulcer located in the distal esophagus is the most common finding in CMV esophagitis (25). The histologic diagnosis is made on biopsies from the ulcer base. Characteristic cytopathic effects include prominent eosinophilic intranuclear Cowdry type A inclusions and cellular enlargement, and occasional granular basophilic cytoplasmic inclusions are found in endothelial and stromal cells deep in the ulcer base (24). The classic inclusion has amphophilic staining with a clear halo around it giving the impression of an “owl’s eye” (25). These differ from HSV infection, since CMV inclusions are mostly found in the glandular epithelium, endothelial cells, and fibroblasts rather than the squamous epithelium. IHC may highlight infected cells without typical CMV morphology. Clusters of macrophages in a perivascular distribution at the ulcer base, though smaller, are also found in CMV infection, similar to HSV esophagitis (25).

Fungal esophagitis

The affected patients are almost always immunocompromised. Fungal esophagitis most commonly results from Candida species, although Histoplasma, Aspergillus, Paracoccidioides, and Cryptococcus can rarely cause esophagitis (1).

Candidal esophagitis

C. albicans is the predominant cause of fungal esophagitis (1). Patients present with acute odynophagia and/or dysphagia in immunocompromised patients (15,23). Most patients also have concomitant oropharyngeal candidiasis (1). Endoscopically, whitish, raised, longitudinal, focal, or confluent plaques or membranes cover a friable mucosa in the mid or distal part of the esophagus. Histologically, erosions and ulcers covered with necrotic squamous debris that contains budding spores and pseudohyphae without true branching and lying perpendicular to the surface epithelium, are seen (23). Invasion of the mucosal or submucosal blood vessels is a common

feature. In the absence of pseudohyphae, oral contamination should be considered before making a diagnosis of candidal esophagitis (22,23). A periodic acid-Schiff (PAS) or methenamine silver stain can be useful when no spores are seen on hematoxylin and eosin (H&E)-stained sections. Parakeratosis and acute inflammation characterized by the presence of neutrophils in the superficial mucosa may call attention to the presence of Candida (22).

Esophagitis in AIDS patients

Though Candida, HSV and CMV esophagitis are common in AIDS patients, a proportion present with large discrete ulcers defined as "giant esophageal ulcers" or "chronic idiopathic esophageal ulcers" in the mid or distal part of the esophagus. Evidence of human immunodeficiency virus (HIV) has been confirmed in these ulcers with a combination of molecular techniques and IHC (23).

Esophagitis and inflammatory bowel disease (IBD)

Esophageal involvement is an uncommon presentation of Crohn's disease. When present, it is usually associated with extra-esophageal disease. The most common clinical presentation is with dysphagia (15,22). Endoscopic findings vary from erosions and aphthous ulcers to punched-out ulcers and strictures (21). Histology is rather nonspecific, with erosions, ulcers and mixed cellular inflammation within the mucosa and submucosa. Granulomas are found in one-third of the cases. Ulcerative colitis may also involve the esophageal mucosa especially in pediatric cases (21,22).

Drug-related esophagitis

The drugs that cause esophagitis comprise antibiotics, nonsteroidal antiinflammatory drugs, iron supplements, potassium chloride, ascorbic acid, azathioprine, and bisphosphonates (1). There is no characteristic finding for drug-induced esophagitis, since the injury results from either a complication of the therapeutic action of the drug or from direct mucosal injury caused by the drug, so-called "pill esophagitis" (22). Pill esophagitis was first described in a patient taking potassium chloride tablets (27). Pills lodge in the mid-esophagus at the level of the aortic arch or in the distal esophagus, where they have prolonged contact with the mucosa. This occurs when the drugs are taken with little or no water (22). The main symptoms are sudden retrosternal pain and painful swallowing. Endoscopically, discrete punched-out ulcer is the characteristic finding of pill esophagitis (27). Most are superficial ulcers that heal readily, except those formed by potassium chloride, which are deep and may even perforate (27). Besides ulcers and erosions, numerous eosinophils may be seen in the squamous epithelium resembling EoE (7). Remnants of the pill may be present at the base of the ulcer in some cases (27).

Caustic esophagitis

Caustic esophagitis results from ingestion of strong alkalis or acids either as a suicide attempt in adults or accidentally in children. Common agents include sodium carbonate, ammonium hydroxide and bleaches. Drain cleaners and detergents are also highly caustic. The extent of injury depends on the amount and type of the ingested agent and the duration of exposure (22). Dysphagia and odynophagia are the main symptoms. Severe corrosive injury leads to hemorrhage, perforation and strictures. The entire mucosa can be separated and extruded in the form of a cast. Damage with alkalis is more severe than with acids since they penetrate the tissue (1). The degree of caustic burns can be graded according to the level of injury within the mucosa, in a similar manner as with skin burns (22).

Radiation/chemotherapy esophagitis

Patients receiving radiotherapy and/or chemotherapy for various malignant tumors may develop esophagitis (1). The extent of injury is determined by the type of treatment, duration, dose, and tissue sensitivity. The spectrum of injury ranges from acute self-limited esophagitis to perforation (22). Patients present with dysphagia and chest pain similar to other causes of esophagitis. In acute cases, mucositis and ulcers can be found, while strictures and webs develop in chronic cases. Histologically, significant atypia with bizarre nuclei and multinucleation is present (2).

Lymphocytic esophagitis

Lymphocytic esophagitis is a recently described variant of chronic esophagitis. It is characterized by extensive lymphocytosis mainly concentrated in the peripapillary zone of the squamous epithelium (1). Patients may have as many as 20-50 lymphocytes/hpf. It has been described in patients with GERD, celiac disease, *Helicobacter pylori* gastritis and Crohn's disease. It may, however, represent a tissue reaction rather than a specific entity (22).

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