Eosinophilic Esophagitis – Pathophysiology and its Clinical Implications

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Abstract:

Classically, Eosinophilic Esophagitis is an antigen mediated chronic disease distinct from gastroesophageal reflux disease. Eosinophilic Esophagitis is an emerging clinical problem that is growing in recognition. It is characterized clinically by feeding dysfunction, dysphagia and reflux-like symptoms. Histologically, Eosinophilic Esophagitis is identifiable by a dense epithelial eosinophilic infiltrate. Experimental modeling and clinical studies over the last decade have greatly improved mechanistic insights and led to improvements in clinical understanding and the assessment of therapeutic options for patients and their clinicians who manage this disease. Here, we review the clinicopathologic diagnostic criteria and our understanding of Eosinophilic Esophagitis as an allergic disease with genetic and immunological components. We present studies defining the importance of the epithelial barrier and the concept of barrier dysfunction as an initiating or perpetuating factor for this disease. We discuss the relationship between the symptoms of dysphagia and feeding dysfunction, our current knowledge of the underlying pathophysiologic mechanisms, and advances in clinical assessment of esophageal distensibility and narrowing in Eosinophilic Esophagitis patients. Lastly, therapeutic implications relating to the advances that have led to our current understanding of the pathophysiology of Eosinophilic Esophagitis are explored.

Introduction

In its healthy state, the esophagus provides for safe passage of nutrition from the mouth to the stomach. This remarkable feat is accomplished by complex innate features of defense that include mucus, bicarbonate, defensins, squamous epithelial cells, and a network of neurons and smooth muscle cells that are arranged in longitudinal and circular fashion. Close inspection of the epithelium reveals an intricate array of stratified epithelia that are closely connected by a series of junctional molecules and interspersed with a number of lymphocytes and other leukocytes such as mast cells. In contrast to the rest of the healthy gastrointestinal (GI) tract where eosinophils are present, eosinophils are absent in the normal esophageal mucosa.

To provide a deep understanding of the clinical features and pathophysiologic mechanisms underlying eosinophilic esophagitis (EoE), it is important to provide historical context of this relatively new disease. Prior to 1960, interrogations of the intestinal mucosa were limited to surgical resections or post mortem analyses. The advent of luminal fiberoptic endoscopy in the 1960's, afforded a new opportunity to develop detailed histologic examination of the GI mucosa. In the 1980's, endoscopic procedures were performed on adults and an increasing number of pediatric patients who had gastroesophageal reflux (GERD) like symptoms. Analysis of mucosal biopsies revealed a pattern of scattered epithelial eosinophilia **(82). Soon thereafter,**

some patients with reflux and other symptoms recalcitrant to acid blockade were found to have a pattern different from that previously associated with GERD, one that revealed dense mucosal eosinophilia of greater than 15 eosinophils per high power field (4, 33, 75). Clinically, these patients presented uniquely from GERD and instead of a history of heartburn or regurgitation, adult patients noted problems with solid food dysphagia and food impaction. In contrast, children with EoE were found to have profound feeding difficulties and in some circumstances, failure to thrive.

Over the course of the last 20 years, a clinical and molecular profile emerged that distinguishes EoE from its counterpart, GERD (57). **Conceptually, a paradigm has arisen that may help to distinguish between these two esophageal diseases. GERD is understood to be a disorder of motility and if complications arise, they likely occur as a result of chronic mucosal inflammation (24, 76). GERD related inflammation could be considered an "outside-in" process in which luminal gastric refluxate initiates and perpetuates epithelial inflammation resulting in an endoscopic appearance of friability and histologically in the disruption of mucosal integrity. In contrast, EoE is conceptually considered, a chronic, allergic inflammatory disorder with symptoms and complications that are related to destructive tissue remodeling. In this paradigm, of an "inside-out"**

disease, allergic inflammation can arise in a genetically predisposed patient in whom chronic antigenic stimulation leads to a type-2 inflammatory response that in some case results in excessive mucosal and submucosal tissue remodeling (57). In contrast to GERD, the endoscopic appearance of EoE is characterized by surface exudate (white plaques), thickened mucosa (linear furrows and edema) and chronic remodeling (rings and strictures) as well as a rubbery texture. In reality, there is likely an overlap between GERD and EoE and the relationship between clinical features and pathophysiological mechanisms continues to be defined(22).

Clinical features and diagnosis of EoE

EoE is diagnosed in patients who have symptoms of esophageal dysfunction with dense esophageal eosinophilia in whom other causes have been ruled out **(38)**. The increasing incidence of EoE in pediatric and adult populations was last estimated at 1 in 10,000 (19). Patients can be affected at any age. EoE is more common in Caucasians and has a clear male predominance (male: female ratio is about 3:1). In addition, EoE accounts for 5-16% of patients with dysphagia, and approximately half of patients with food impaction **(20)**. Approximately 30-60% of patients have comorbidity for one or more classical allergic disorders, such as bronchial asthma

and food allergy (59). EoE related symptoms differ between young patients (infants and children) and adults (38). Infants and children often exhibit a wide range of nonspecific symptoms such as feeding difficulty, reflux and vomiting. Thus, clinical recognition of EoE in children may be more difficult than in adults. Teenagers and adults, develop stereotypical patterns of solid food dysphagia, food impaction and chest pain. On the other hand, symptoms resembling GERD, such as heartburn and precordial pain, are common regardless of age. Symptoms may be underestimated by the patient's adaptation (long mealtimes, preference for minced foods, frequent drinking during meals)(52). It is unclear whether these symptomatic differences reflect the ability to report symptoms, duration of illness or different pathophysiology of disease (68).

In order to properly diagnose EoE, various diseases such as GERD, esophageal cancer, achalasia, hypereosinophilic syndrome, infection, Crohn's disease, and drug allergies need to be ruled out. Of these, the major challenge lies in differentiation from GERD and addressing the previous diagnostic guidelines requiring empirical treatment of high dose proton pump inhibition (38). Since the original diagnostic consensus recommendations were published, it has become clear that proton pump inhibitors (PPIs) exert a significant impact in reducing symptoms and esophageal eosinophilia in

patients. Such patients have been termed to have PPI-Responsive Esophageal Eosinophilia (PPI-REE). The last decade's worth of clinical experiences and research showed that many of these patients exhibit no obvious differences in clinical or molecular profiles when compared to those who have classical EoE (47). Therefore, patients described as having PPI-REE may actually represent a subset of patients with EoE who respond to PPIs. Thus, the trial of PPI has been excluded from diagnostic recommendations (22, 39). The implications of this change are significant and include decreased exposure to PPIs, reduction in time to diagnosis, fewer endoscopies to establish diagnosis and a deeper understanding of treatment naïve esophageal mucosa.

Allergies and genetic impact on EoE phenotypes

In 1996, Kelly et al. reported the first series of children with EoE and made the seminal observation that symptoms and histopathology responded to an amino acid based diet and upon **food** reintroduction, symptoms and epithelial eosinophilia returned (33). This finding provided the first evidence that esophageal eosinophilia may have an underlying allergic etiology. Since then, a number of prospective trials of food elimination documented the ability of dietary restriction to induce histologic remission of EoE in upwards of 43% - 74% of children and adults **(49). Peripheral**

eosinophilia is found in 40-50% of patients (38). In addition, a number of clinical studies further characterized the allergic phenotype of patients with EoE identifying that between 28-86% of adults, and between 42-96% of pediatric patients may be affected by one or more co-morbid allergic diseases such as atopic dermatitis, food allergies, asthma or allergic rhinitis (38).

Studies examining the molecular underpinnings of EoE focus on **chemokine's** known to be related to eosinophilia **(e.g. eotaxin-3)** and **type 2 cytokines (e.g. IL-5 and IL-13)**. **Microarray** analysis using esophageal specimens reveal that eotaxin-3 has the largest fold change in mRNA expression level between EoE patients and controls. In addition, eotaxin-3 expression in tissues strongly correlates with tissue eosinophil and mast cell counts (9). IL-5 participates in eosinophil maturation and eventual migration into the esophageal epithelium and IL-5 mRNA and protein is increased in the esophagus of EoE patients**(73)**. Subsequent studies examined the role of IL-5 in murine models of EoE demonstrating a key role for IL-5 in esophageal eosinophilia (45). Similarly, IL-13 is increased in tissue sections of EoE patients and stimulation of esophageal epithelia with IL-13 leads to the production of eotaxin-3, a major eosinophil chemotactic factor as well as diminished expression of filaggrin **and results in** decreased esophageal barrier function (6, 8). Using a translational approach, **Cianferoni et al.** found that Th2 cells expressing IL-4,

IL-5 and IL-13 significantly increased in peripheral blood in the active phase of EoE patients who did not have milk-specific IgE (15), **further implicating type 2 immunity as a target for treatments in EoE. Several therapeutic trials have targeted type 2 cytokines in EoE to limited success. T**rials using anti-IL-5 **and anti-IL-13** antibodies **both** document **their** ability to diminish **esophageal eosinophilia**. Despite these impressive findings, these studies did not support clinical use because they were unable to meet the endpoint of symptom reduction (29, 61, 71, 74). Clinical trials of anti-IL-4Rα (dupilumab) are in progress (NCT02379052).

In order to provide a unbiased approach, a genome wide association stud**ies** (GWAS) provided further support for an underlying allergic/Th2 cytokine mechanism for EoE **(66, 70)** In these stud**ies, single nucleotide polymorphisms (SNP) in the TSLP locus were identified in EoE subjects but not controls.** TSLP expression is increased in esophageal tissues of EoE patients. TSLP acts on dendritic cells evoking a Th2 dominant immune response. Artis et al provide confirmation of a role for TSLP in the underlying pathogenesis of esophageal eosinophilia (55). In this study, inhibition of TSLP led to the reduction food impactions and eosinophilia in an EoE mouse model.

An emerging body of evidence supports the association of immunoglobulin patterns in EoE. For instance, IgG4 is increased in EoE tissues

(16, 65). Despite earlier hope that IgE mediated mechanisms may provide diagnostic, therapeutic and pathogenetic insights for EoE patients, a growing body of evidence does not support its direct role. Mouse models of EoE demonstrate the ability of B cell-deficient mice to develop esophageal eosinophilia(46). IgE is not elevated in all EoE patients and when increased, it is difficult to ascertain whether it is due to EoE or other underlying allergic conditions. Omalizumab, an anti-IgE monoclonal antibody, was not effective in inducing remission of EoE(16).

The impact of epigenetics and environmental factors on EoE continues to emerge. Caesarian section, preterm birth, exposure to antibiotics in infantile period, reduced breast feeding, and living in less crowded area have all been linked to an increase of EoE (30, 31). As with the increase in other allergic diseases, the “Hygiene Hypothesis” may also help to explain the recent increase in EoE. Decreased exposure to bacteria within 2 to 3 years after birth can evoke Th2-dominant immunological status, and thus a propensity to develop allergic disease (31, 77). Based on similarity to the other classical allergic disorders, such deviation of Th1/Th2 balance stemming from the change in lifestyle could relate to the increase in EoE. For example decreased bacterial exposure in infancy and childhood may relate to the decreased rate of *Helicobacter pylori* detection in the general population (44). Such decreases are especially prominent in developed countries, where the incidence of

EoE appears to be high. At least one study demonstrates that the infection rate of *Helicobacter pylori* is inversely correlated to esophageal eosinophilia, but it is unclear whether there is direct causative relationship or not (23). A recent study did not find this same association indicating the need for more epidemiologic and mechanistic studies (48).

Barrier dysfunction; the chicken or the egg of the EoE story?

A number of hypotheses have been raised regarding diminished esophageal barrier function in EoE. First, some patients with EoE may have diminished epithelial barrier at baseline when not inflamed thus predisposing them to allergic sensitization or challenge; this model is similar to that seen in atopic dermatitis. **Indeed,** transcriptional alterations **have been found** in human chromosome 1q21, which encodes for a group of genes related to epidermal differentiation including filaggrin (8) and another tissue specific proteolytic molecule, calpain14 (35). Altered expression of these genes may predispose to barrier dysfunction at baseline or **after** activation by **Type 2** cytokines such as IL-13 (8). A recent translational study measured the esophageal **barrier using impedance monitors in adult EoE patients before and after treatment (80).** They determined that following treatment, esophageal barrier

was still reduced compared to normal values indicating a potential innate barrier defect.

Second, the impaired barrier may develop as a result of peptic or other injury. This hypothesis, termed the “two-hit hypothesis”, is based on the clinical observation that EoE may develop after an epithelial insult from acid injury, trauma or infection (13, 27). In this circumstance, food or aeroallergens may then contact the damaged epithelium and sensitized microenvironment in the esophageal mucosa leading to activation of a **type 2 inflammatory** pathway.

Finally, barrier dysfunction may occur as a self-perpetuating product of ongoing inflammation. In this circumstance, once an inflammatory process starts, the epithelial surface may become increasingly permissive and allow more allergenic stimulation to penetrate and develop an ongoing allergic cycle. Support for this paradigm is based on histological findings of actively inflamed tissues that demonstrate dilated intercellular spaces (Figure 2) and decreased desmosomes, as well as abnormal impedance measurements in inflamed tissue compared to normal (10, 79).

All of these hypotheses may help to explain part of the barriers’ role in EoE, and several lines of evidence dissect the underlying associated pathways using various model systems. Translational studies utilizing impedance monitors **and**

Ussing chamber studies reveal that the barrier is leaky during active inflammation compared to inactive disease (80). Gene arrays laid the basis of several mechanistic studies demonstrating the importance of IL-13 in barrier dysfunction. IL-13 downregulates filaggrin and desmoglein-1 and upregulates calpain 14, all of which can contribute to diminished barrier. Filaggrin deficiency is also noted in patients with atopic dermatitis (58), another allergic disease associated with dysfunctional barrier. Genetic silencing of desmoglein induced barrier disruption *in vitro* (67). GWAS studies highlighted increased CAPN14 expression associated with a subpopulation of EoE (35), while *in vitro* culture of esophageal epithelial cells with IL-13 led to increased CAPN14 expression and a subsequent loss of barrier function **implicating its importance in barrier dysfunction in EoE** (18). In addition to its role in remodeling, TGF-β1 also decreased epithelial barrier function *in vitro,* by mediating a decrease in the expression of the tight junction molecule Claudin 7 (53). Taken together, the role of an intact barrier is likely critical to disease processes in EoE.

Relationship of dysphagia and feeding problems with esophageal remodeling in EoE

Dysphagia, in adults, and feeding problems, in children, are some of the most common presenting symptoms of EoE (52) that may relate to dysmotility or excessive

remodeling. Both of these symptoms **pose** significant challenges for the evaluation and treatment of EoE patients. Patients often develop coping mechanisms to limit symptoms. Instead of reporting difficulty swallowing, they may self-limit themselves from eating highly textured foods that are difficult to swallow such as bread, steak or rice. Parents may report excessively prolonged mealtimes due to drinking copious amounts of water or chewing food excessively, often to the point of pulverization. **These symptoms pose the practical problem related to caring for a child who may take hours to feed a meal or limiting social exposure because of embarrassment. They also create a barrier to completing therapeutic studies in which this type of symptom has been difficult to measure.** Over the last few years, symptom assessments for adults with EoE have been developed that take this symptom into account (63). Other metrics to assess disease status which incorporate the remodeling that occurs with chronic inflammation include barium esophagrams with pill (43), endoscopic scoring of the mucosal surface (81), histological assessments (17) and most recently catheter based measurement of esophageal distensibility (42).

The underlying pathogenetic mechanisms that explain these symptoms are not yet certain but early clinical studies suggested these problems **might** result from overabundant remodeling of the epithelium, lamina propria, vasculature and the

deeper esophageal wall, or to disordered motility (26, 56). Remodeling in itself is a necessary and critical part of host defense, but in excess can result in pathological outcomes. For instance, the esophageal lumen in some patients with EoE is partially **occluded due to either isolated, focal or diffuse, longitudinal stricture formation. The classical histological findings of EoE include esophageal eosinophilia and rete peg elongation. Additionally, evidence of dense collagen fibrils in the lamina propria may represent problematic scarring. A number of molecules have been implicated as targets of esophageal remodeling including mediators such as TGF-β1, CCL-18, and FGF-9.** Fibroblast activation occurs in response to TGF-β1 *in vitro* leading to the secretion of fibrotic factors such as collagen and fibronectin (50, 60). Epithelial and sub-epithelial fibrosis has also been noted in EoE (12), with epithelial cells themselves contributing to remodeling through mechanisms such as epithelial-mesenchymal like transitions in response to factors including TGF-β1 (32, 50, 51). Increased vascular density and expression of activation markers has been noted in EoE patients (2), while pre-clinical models treated with anti-eosinophil (62) and anti-GM-CSF (41) reveal reduced vascular remodeling, implicating remodeled vasculature as a response to chronic inflammation in EoE. Cytokine involvement in the pathophysiology of EoE is also supported by the effects of cytokine targeted drugs (anti-IL-5, anti-IL-13) on epithelial eosinophil

chemoattractant CCL26 production and **subsequent** esophageal eosinophilic infiltration (3, 7, 14, 45, 61, 74) Finally, exposure of esophageal smooth muscle cells to TGF-β1 leads to smooth muscle cell activation *in vitro*, resulting in increased contraction (1, 5, 60).

New technology has brought more understanding of the functional aspects of this esophageal remodeling. Functional Luminal Imaging Probe (FLIP) is a catheter-based technology that upon volume-based insufflation permits measurement of esophageal compliance. Results from studies using this device in adults demonstrate decreased distensibility in patients with EoE compared to controls (37, 54). In children with EoE, distensibility was decreased compared to normal controls and improved following treatment (42). Moreover, longitudinal studies have demonstrated that treatment with either steroids or diet elimination improves distensibility. These studies also demonstrated that improved distensibility correlated with patient reported symptom severity indices possibly more so than the traditional marker of histological marker of disease severity, eosinophils/hpf (11). Evaluations of distensibility potentially offer a predictive quality as shown in an adult study in which, a threshold distensibility plateau predicted the likelihood of food impaction (54). What is unknown however, is what specific remodeling features have the greatest impact on the observed differences in esophageal compliance and, more specifically, what

therapeutic target(s) that are affected during successful treatments. With respect to motility, the incidence of dysmotility is high in long-term EoE patients (78), In EoE patients, longitudinal muscle contractility is associated with impaired peristalsis and is suspected to be associated with dysphagia (34). Submucosal mast cells found in EoE patients may enhance the contractility of esophageal smooth muscle (1). In mouse models of EoE, dysmotility of the esophagus similar to that of EoE patients was observed (40).

Natural history of EoE and impact of therapeutic interventions

EoE was reported in the early 1990's but Consensus Recommendations **for diagnosis** were **first** published in 2007 (28). Thus, few studies document long-term outcomes of this disease. **As clinical experiences increase, phenotypic patterns have been increasingly recognized.** For instance, while most children experience normal growth, some may be found to have malnutrition. To date, no pre- or malignant potential has been observed but food impactions are common occurrences. Food impactions develop in upwards of 30 to 45% of patients and are often the presenting symptom leading to diagnosis (69, 72). **Determination of the exact incidence of stricture depends on how stricture or fibrostenosis is defined. However, upwards of 67-70% of untreated patients were found to develop**

strictures and in another study, 9% of subjects were found to have an extremely narrow caliber esophagus (inability to pass a standard adult endoscope) (25, 64, 69). Older age and duration of inflammation are currently considered the most notable risk factors for having a stricture. For example, in the pediatric population, fibrostenotic features are reported in up to 16% of the population and impaction in up to 21% (21, 69).

In an effort to provide optimal outcomes, goals of treatment with diet **elimination of food triggers and topical steroids include reduction of symptoms and improvement of esophageal eosinophilia**. Whether or not these approaches will alter the natural history of the disease is not certain**. However,** statistical modeling of untreated disease suggests an increasing likelihood of developing strictures and that prolonged use of topical steroid may prevent food impaction (21, 36). In a cohort study of just over 200 adults with EoE, 9.1% developed food impactions during follow up periods in which they had stopped topical steroid treatment**. In contrast,** only 3.5% experienced food impactions when using topical steroid treatment greater than 50% of the time**,** and even fewer (1.7%) experienced food impaction when taking treatments >75% of the time (36). While swallowed topical steroids have demonstrated the ability to impact inflammation, improve symptoms and prevent complications of EoE when used consistently, adherence to treatment in the

management of chronic disease remains challenging. Additional options, including biologics such as anti-IL-5 or IL-13 provide hope for alternative approaches.

Summary

In the past two decades since the **observation** of EoE was first **reported,** the clarification of its pathophysiology has **advanced**. EoE is a chronic disease with a unique gene expression pattern and an increasingly clear understanding of the pathophysiology of eosinophil migration, barrier dysfunction and fibrosis has been elucidated. Therapeutic interventions such as topical steroids may alter the natural history of EoE even after treatment termination. **Based upon a deeper understanding of the** pathologic **processes of EoE, we as a field** will develop molecule-targeted therapeutic options with fewer side effects and **ultimately** better medical management **of patients with EoE**.

Figure Legends

Figure 1

Endoscopic findings associated with EoE. A. Normal esophagus- smooth, pink, lacelike veiled vascular pattern, B. Linear furrows extending longitudinally with loss of vascular pattern and epithelial edema, C. White exudates representing eosinophilic pus, D. Longitudinal tear that represents a fragile mucosa. This feature can occur with the mere passage of the endoscope.

Figure 2

Histological patterns associated with EoE. A. In the left low power image, infiltration of eosinophils and epithelial hyperplasia and microabscess (within the circle) can be seen. B. In the right high power image (from different patient), rete peg elongation (arrow) and the expansion of intracellular space, so-called spongiosis (within the circle) is prominent in addition to numerous eosinophilic infiltration.

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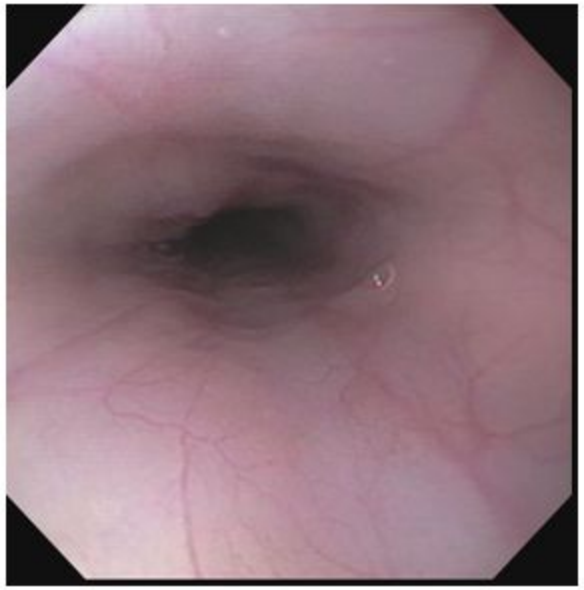
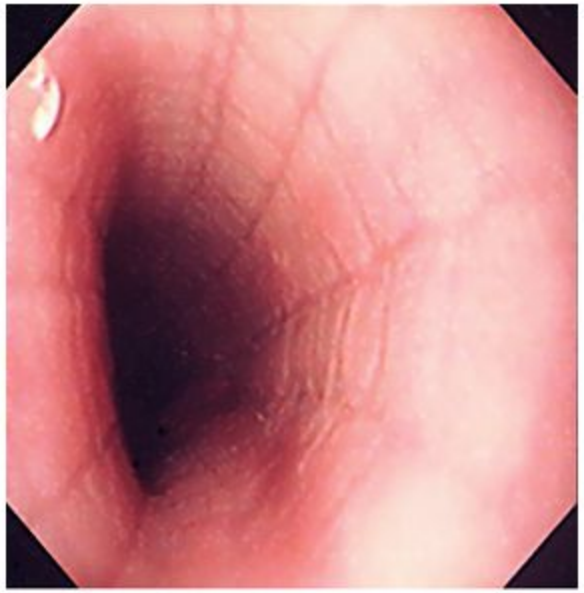
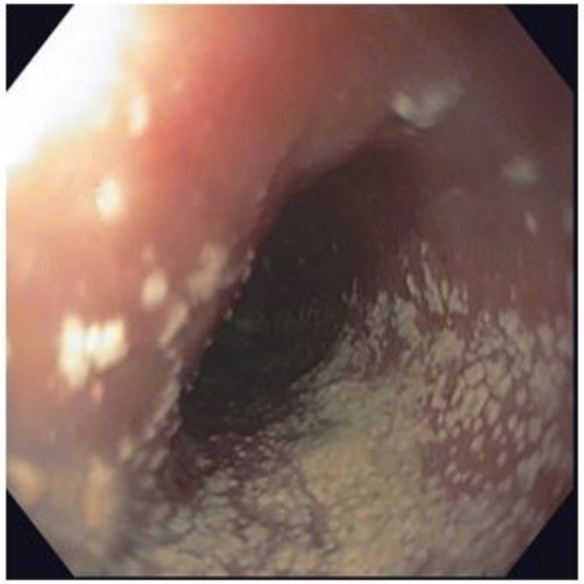
Figure 1



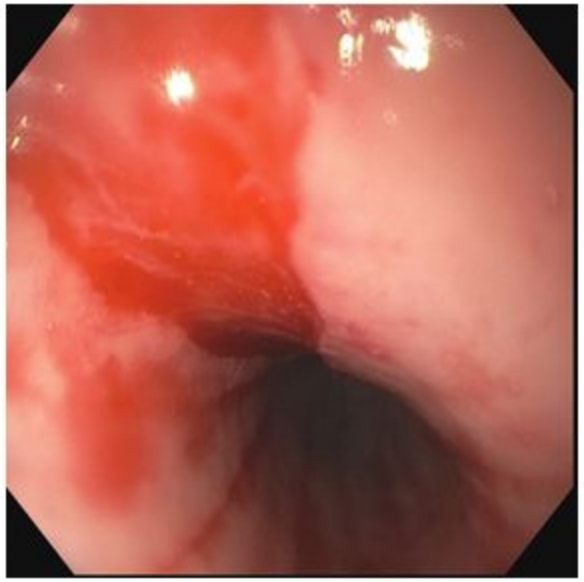
A. Normal



B. Linear furrows



C. White exudate



D. Longitudinal tear

Figure 2