



Eosinophilic Esophagitis Clinical Manifestations and Differential Diagnosis

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Abstract

As a chronic inflammatory disease with eosinophilic infiltrate of the esophagus, eosinophilic esophagitis (EoE) causes a variety of gastrointestinal (GI) clinical manifestations. None of the symptoms, endoscopic features, or biopsy findings is pathognomonic of the disease, even with high degrees of esophageal eosinophilia. The pathogenesis has been explored by several studies, yet it still far from being completely understood. Evidence supports a role of allergen-driven Th2 lymphocyte mechanism, though not in every patient. This article addresses the disease's clinical manifestations, endoscopic findings, diagnosis, and differential diagnoses. In addition to the current diagnostic criteria, we summarize some recently emerging procedures that promise of enhancing more precise diagnosis and institution of early appropriate management, with consequent better quality of life and reduction of complications.

Keywords Eosinophilic esophagitis · Eosinophilic diseases · Gastrointestinal allergy · Gastrointestinal disorders · Food allergy

Introduction

Eosinophilic esophagitis (EoE) is a chronic disease of the esophagus that can clinically manifest as feeding difficulty, vomiting, failure to thrive, epigastric pain, and food impaction. Because its symptoms and pathologic findings are not pathognomonic, it was misdiagnosed until it was recently described as a specific disease entity. The first reported case was in 1977 about esophageal eosinophilia in an adult with asthma and allergic rhinitis who presented with chronic dysphagia and globus [1]. It was not until 2007 that the first guidelines for diagnosis and management of EoE were developed [2]. Understanding of the disease pathogenesis was mostly derived from pediatric studies. In adults, EoE is mostly misdiagnosed as reflux or diagnosed at a severe stage and is more associated with complications. The discovery of the disease's genetic profile [3, 4] and transcriptome [5] helped to

better understand the mechanism of the disease which is being increasingly encountered by both the allergists and the gastroenterologists. This review will focus on the clinical manifestations and differential diagnosis of the disease.

Definition and Epidemiology

EoE is a chronic, immune-mediated clinicopathological disease, characterized by symptoms related to esophageal dysfunction with predominantly eosinophilic inflammation [6, 7]. The epidemiology of EoE has been addressed by a few studies [8–12]. The reported prevalence varied widely probably due to differences in multiple factors such as clinical and laboratory criteria, patients' ages, duration of illness, and geographic variation in dietary habits.

In 2016, Arias et al. [12] published an extensive systematic literature review on the epidemiology of EoE reported from various countries. The overall prevalence was 22.7 cases per 100,000 inhabitants, being highest in North America with a prevalence of 30.7 cases per 100,000 inhabitants. The estimated pooled incidence was 3.7 per 100,000 inhabitants/year, being higher in adults than in children (7 vs 5 per 100,000). A dramatic increase was noted after the publication of the consensus recommendations for diagnosis and management of the disease in 2007 [2].

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EoE is becoming one of the most prevalent esophageal diseases, which can be due to increasing recognition. From an epidemiological stand point of view, the reports are showing a steady increase in incidence. A retrospective review of pathology specimens in the USA implicated that EoE was present in a large number of patients prior 1999 although the disorder was unrecognized at that time [13, 14]. A retrospective study from Switzerland showed that the overall incidence of EoE between 2010 and 2013 was ten times higher than between 1993 and 2009. The overall incidence was 6.3/100,000 people and a cumulative prevalence of 24.1/100,000 people [15].

Similar findings were reported in a Danish retrospective study using the national database over a 15-year period [9]. Compared to the year 1997, a 19.5-fold increase in the diagnosis of EoE, reaching a prevalence of 13.8/100,000 by 2012, with males more affected than females (prevalence 24.6 vs 9.2/100,000). EoE has been more frequently reported in Caucasians than in other ethnicities [8]. African-Americans with EoE are often diagnosed later in life and have more reflux symptoms than dysphagia or food impaction [16, 17].

Pathophysiology and Etiology

The pathognomonic lesion of EoE is predominantly eosinophilic inflammation mediated by Th2 lymphocytes with varying degrees of involvement of basophils, natural killer T cells, and mast cells [18]. Eosinophils are the primary effector cells and along with IL-13 have been found to drive fibrosis and strictures [19]. Peripheral eosinophilia has been found in 50% of patients and elevated IgE level in about 60% [20].

Although the etiology of EoE is not completely understood, there is definitely a role for food allergens in its pathogenesis. Multiple studies have identified food allergens as triggers of EoE in both pediatric and adults [21]. The most strong evidence of food allergen-driven EoE is that amino acid formulas can be a highly effective therapy [22]. There is also clinical and histological remission with elimination diet and relapse with reintroduction of the offending food [23–25]. However, such interventions are not always effective for all patients, suggesting there are other possible causes. Pollens have also been implicated in the pathogenesis [26], which may be partly due to cross-reactivity with certain food allergens [27]. Even though patients with EoE have higher rates of positive testing for food-specific IgE, EoE seems to be predominantly a non-IgE-mediated reaction. In support of this is the failure of omalizumab therapy in some cases [28]. Furthermore, the clinical and histological features in EoE patients with associated atopic disease were not different from those without atopy [29].

Additionally, patients with esophageal atresia have a higher incidence of EoE [30, 31], which may be explained by their inherent esophageal dysmotility resulting in a longer contact of food with the esophageal mucosa and possible increasing

allergic sensitization [32]. Specific genetic similarities between esophageal atresia and EoE have been proposed [30].

Clinical Manifestations

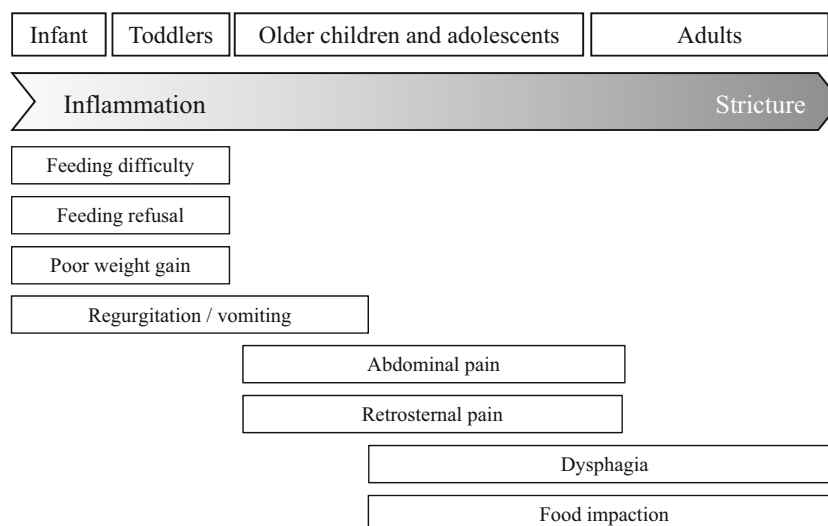
Although EoE can affect all ages, the clinical presentation varies with age and the patient's ability to communicate symptoms [33] (Fig. 1). Children may have a wide variety of non-specific symptoms due to esophageal motility dysfunction. Most common manifestations in infants are feeding difficulties such as gagging, delay in advancing solid food introduction, and food refusal. Infants and small children might also present with failure to thrive. In a small retrospective study, which included 62 pediatric patients, failure to thrive was present in 24% [34]. Older children usually complain of nausea, vomiting, or epigastric pain [18, 35]. However, chest pain, sialorrhea, sleep disturbances, or respiratory complaints have also been described [33]. Undernutrition is uncommon in adult patients who can easily cope with dietary restrictions [33]. In a large prospective study in adults with EoE, body mass index was somewhat lower than that in controls, but not low enough to be considered underweight [36].

Chronic reflux symptoms and dysphagia can be present in all age groups [6]. Adolescents and adults are more likely to present with dysphagia to solid foods, starting as an unpleasant feeling during swallowing and may escalate to episodes of food impaction. Dysphagia has become the most common symptom that leads to endoscopy. It has been reported that between 50 and 70% of patients with dysphagia had EoE [37–40]. Food impaction should alert clinicians about the possibility of EoE [33]. It has been reported in 50% of children [41] and 33% of adults [42] undergoing endoscopy for food impaction removal. Patients with food impaction usually present with acute severe retrosternal chest pain. Spontaneous esophageal rupture from forceful retching is a rare but serious complication manifesting with severe vomiting, chest pain, and pneumomediastinum (Boerhaave's syndrome) [43, 44].

Seasonal variation regarding diagnosis or exacerbation of symptoms has been reported. The number of newly diagnosed cases of EoE was noted to be significantly lower during winter [45] than in the summer, which might be relevant to the pollen season [46, 47]. However, a meta-analysis found no statistical difference between season of the year and the new diagnosis or worsening of symptoms [48]. Such a discrepancy may be, at least partly, due geographical variations and differences in the study methodology.

Associated Atopic Disorders

Patients with EoE usually have family history of atopy. They also have asthma, allergic rhinoconjunctivitis, or atopic

Fig. 1 Eosinophilic esophagitis symptoms according to age

dermatitis in up to 80% [49–51]. These observations, among others, support the inclusion of EoE among allergic disorders. History of esophageal symptoms (dysphagia and/or food impaction) in an atopic patient should arise the possibility of EoE [32].

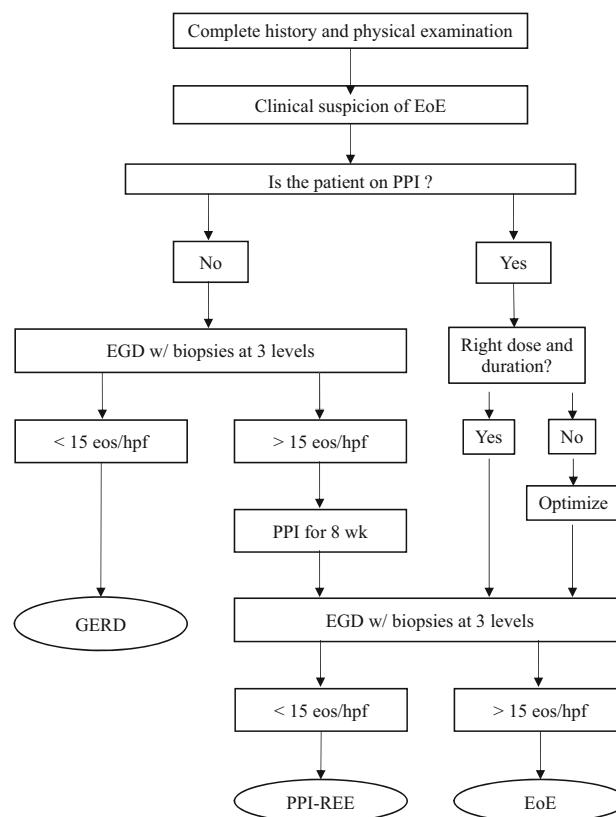
Evaluation and Diagnosis

Medical History

The constellation of symptoms in EoE is mainly gastrointestinal and varies according to the patient's age, duration of illness, and severity of symptoms (Fig. 1). In infants and young children, the disease presents primarily as feeding difficulties or failure to thrive. Older children and adults may notice dysphagia related to swallowing a lump of food that usually resolve by drinking a liquid. Since the disorder is not IgE-mediated, rarely, certain patients suspect relationship between the symptoms and specific foods. Because symptoms are mostly non-specific, guidelines for diagnosis of EoE have been developed and include endoscopic and biopsy findings [2, 7, 20]. A diagnostic algorithm is presented (Fig. 2).

Guidelines for the diagnosis and management have been developed and periodically updated (Table 1). The first consensus guidelines were published in 2007 [2], which emphasize the importance of esophageal symptoms together with a peak esophageal eosinophilia of > 15 cells in any high-power field. It stated that a trial of acid suppression or a distal esophageal pH study helps exclude gastroesophageal reflux disease (GERD). In 2011, an updated version [20] introduced the term proton pump inhibitor-related esophageal eosinophilia (PPI-REE) to the guidelines and recommendation about topical corticosteroid therapy. Later in 2013, the guidelines by the American College of Gastroenterology [52] emphasized the

importance of excluding secondary causes of mucosal eosinophilia and introduced the concept of response to treatment



EoE = eosinophilic esophagitis, PPI = proton pump inhibitor, EGD = esophagogastroduodenoscopy, eos/hpf = eosinophils per high power field, GERD = gastroesophageal reflux disease, REE = responsive esophageal eosinophilia. Modified from ESPGHAN Guidelines [53]

Fig. 2 Diagnostic algorithm for eosinophilic esophagitis. EoE, eosinophilic esophagitis; PPI, proton pump inhibitor; EGD, esophagogastroduodenoscopy; eos/hpf, eosinophils per high-power field; GERD, gastroesophageal reflux disease; REE, responsive esophageal eosinophilia. Modified from ESPGHAN Guidelines [53]

Table 1 Summary of EoE guidelines developed over the years 2007 to 2017

	Consensus guidelines 2007 Furuta et al. [2]	Consensus guidelines 2011 Liacouras et al. [20]	ACG 2013 Dellon et al. [52]	ESPGHAN 2014 Papadopoulou et al. [53]	European Committee 2017 Lucendo et al. [7]
Definition	Clinicopathologic disease characterized by esophageal symptoms with esophageal eosinophilia not associated with GERD	Chronic, immune/antigen--mediated esophageal disease characterized by symptoms of esophageal dysfunction and eosinophilic inflammation in the esophagus	Clinicopathologic disorder characterized by esophageal dysfunction, esophageal eosinophilia (peak > 15/hpf) persistent after PPI trial and secondary causes excluded	Chronic, immune/antigen--mediated esophageal disease associated with esophageal dysfunction from severe eosinophilic--predominant inflammation	Chronic, local, immune-mediated esophageal disease characterized by esophageal dysfunction and eosinophil-predominant inflammation after excluding other causes of eosinophilia
Diagnosis	Pathological pH monitoring is equivalent to PPI response or GERD Multiple biopsies needed Peak eosinophil count > 15/hpf	Introduction of the term PPI-REE 2–4 biopsies of proximal and distal esophagus Peak eosinophil count > 15/hpf	Response to treatment (diet or topical steroids) is supportive of diagnosis 2–4 biopsies of proximal and distal esophagus Peak eosinophil count > 15/hpf	Dietary treatment for 4–12 weeks is a therapeutic option in children with EoE 2–4 biopsies of proximal and distal esophagus Peak eosinophil count > 15/hpf	EoE and GERD are different entities and may coexist At least 6 biopsies from different locations Peak eosinophil count > 15/hpf
Treatment	No consensus of dose of topical steroids	PPI for 8–12 weeks; 20–40 mg once or twice a day in adults and 1 mg/kg twice daily in children Fluticasone ^a children: 88–440 µg twice to 4 times daily adults: 440–880 µg twice a day Budesonide ^b children < 10 years: 1 mg daily older children and adults: 2 mg daily	Persistent esophageal eosinophilia after 2 months of PPI is diagnostic Fluticasone ^a children: 88–440 µg/day in divided doses adults: 880–1760 µg/day in divided doses Budesonide ^b children: 1 mg/day in divided doses adults: 2 mg/day in divided doses	PPI trial for 8 weeks in children with esophageal eosinophilia is recommended with subsequent EGD under PPI therapy Fluticasone ^a children: 88–440 µg 2–4 times a day teens and adults: 440–880 µg twice daily Budesonide ^b children < 10 years: 1 mg/day in divided doses older children and adults: 2 mg/day in 2 divided doses	PPI, diet, and topical steroids might be offered as first line therapy. Choice of therapy should be individualized

ACG = American College of Gastroenterology; ESPGHAN = European Society of Paediatric Gastroenterology, Hepatology and Nutrition; PPI = proton pump inhibitor; REE = responsive esophageal eosinophilia; hpf = high power field; GERD = gastroesophageal reflux disease. metered-dose inhaler puffed into the mouth during a breath holding and swallowed; swallowed solution mixed with a thickening agent (e.g., artificial sweetener)

(dietary elimination or topical steroids) as supportive of the diagnosis.

It is not uncommon for patients referred for evaluation to be already receiving PPI. According to the European Society of Pediatric Gastroenterology, Hepatology and Nutrition [53], if the patient is on an adequate PPI therapy and the endoscopic and histologic findings are consistent with EoE, the diagnosis should be settled without the need of having a second endoscopy. Improvement in symptoms should be supported by biopsy findings. Most recently, the guidelines have been updated by a Working Committee from the United European Gastroenterology, the European Academy of Allergy and Clinical Immunology, the European Society of Pediatric Gastroenterology, Hepatology and Nutrition, and the

European Society of Eosinophilic Oesophagitis [7]. The Committee cautioned against the reliability on symptoms improvement alone and recommended obtaining a minimum of six biopsies.

Endoscopy and Histology

Upper GI endoscopy may reveal esophageal mucosal abnormalities in the form of edema (mucosal pallor and decreased vascular markings), white spots or plaques (eosinophilic microabscesses), fixed rings (feline folds or trachealization), longitudinal furrows, and in severe cases, strictures [7, 20, 54] (Fig. 3). The mucosal inflammation may be severe with the appearance of crepe paper, and the passage of the endoscope

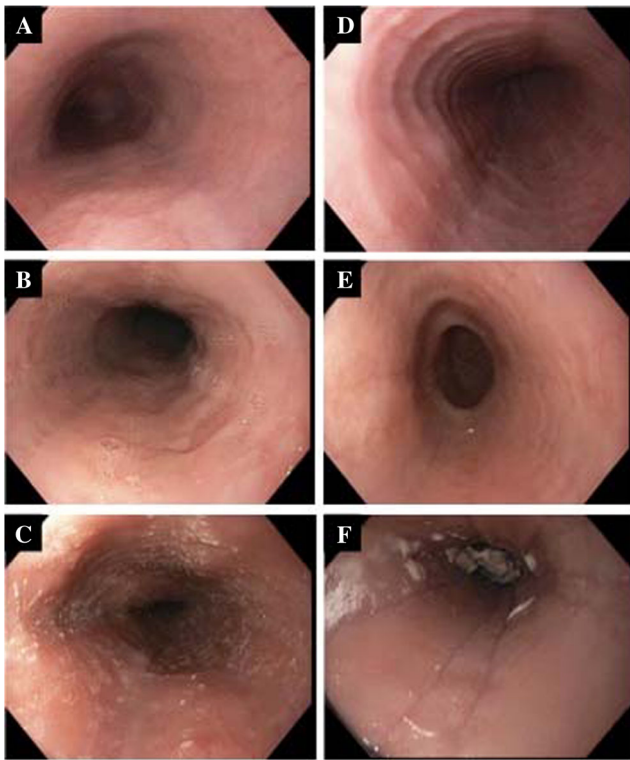


Fig. 3 Endoscopic features of eosinophilic esophagitis. **a** Normal esophageal mucosa. **b** Pale mucosa with loss of vascular markings. **c** White patches consistent with eosinophilic abscesses. **d** Pale mucosa with circular rings. **e** Two fixed ring-like strictures. **f** Meat bolus impaction at mid esophagus with longitudinal furrows and pale mucosa

may cause tears and bleeding [55]. On the other hand, in chronic cases, the mucosa can be tough and pose resistance in obtaining biopsies. The so-called *pull sign* has been noted to have a 98% specificity and a 97% positive predictive value for EoE [56].

Recently, some authors proposed an endoscopic classification and grading system called Endoscopic Reference Score for assessment of EoE activity that showed good inter-observer agreement [57, 58]. It is based on the presence and severity of fixed esophageal rings, exudate (white spots), furrows, edema, and strictures. Esophageal rings and furrows were reported to be more common in Caucasian than in African-American patients. Strictures are more common in adults than in children [16, 59].

Biopsies should be taken from several levels of the esophagus, at least two samples from each site [7, 20]. They should be obtained even when the mucosa visually appears normal. A large meta-analysis study revealed that the mucosa appeared normal by endoscopy in 7–17% of biopsy-proven EoE patients [60]. In certain areas, dense eosinophilic infiltrates may appear as microabscesses. Other histological features may include extracellular eosinophil granules, basal cell hyperplasia with resulting acanthosis, papillary elongation, and lamina propria fibrosis. (Fig. 4) In addition to eosinophils, there is often increased numbers of mast cells, B-lymphocytes,

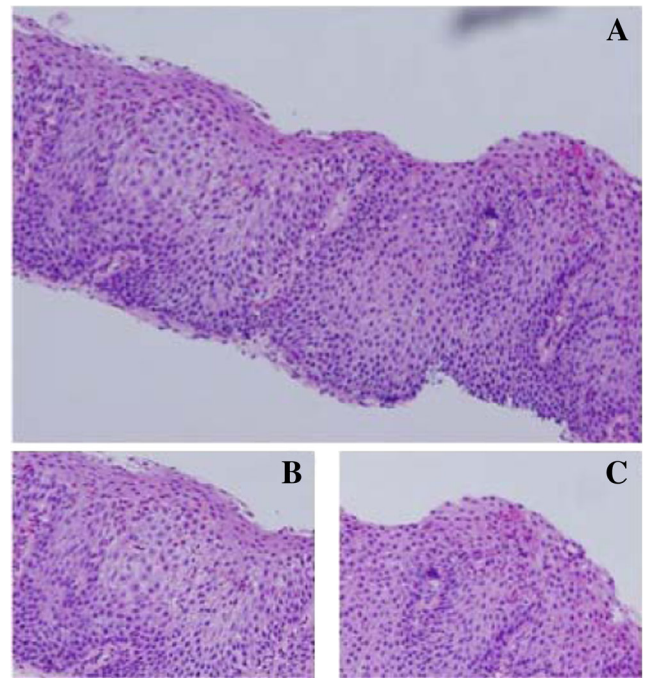


Fig. 4 Esophageal mucosal histology in eosinophilic esophagitis. Microphotography of esophageal biopsies with hematoxylin and eosin stain from a 12-year old boy with history of chronic dysphagia to solid foods and meat bolus impaction. **a** Low-power view shows elongation of the papillae and intra-epithelial eosinophils. **b** High-power view shows spongiosis of the epithelium. **c** High-power view shows degranulation of eosinophils

and immunoglobulin-bearing plasma cells [61, 62]. If the patient was already on PPI therapy and the eosinophils are < 15/hpf, the diagnosis of EoE may be based on the presence of extracellular eosinophil granules [20].

It is generally recommended to obtain biopsies from the gastric antrum and duodenum to rule out other diseases or to know whether the eosinophilic disorder is limited to the esophagus or involves other parts of the GI tract [20].

Whereas eosinophils are absent in normal esophageal mucosa, they are present in various numbers in the rest of the gastrointestinal tract [63]. Hence, an abnormal number rests on the expertise of the pathologist.

Radiologic Imaging

In certain patients, esophagram may be useful in assessing the length and diameter of the esophagus. EoE should be considered if multiple, closely spaced, concentric ring-like indentations or a smooth, luminal narrowing of variable lengths are noted [64]. Fluoroscopic upper gastrointestinal studies have low sensitivity in diagnosing EoE. It was normal in 71% of patients, including a few who had acute food bolus impaction [65]—a finding that suggests dysmotility rather than a fixed stricture is causing the impaction. Similarly, the Cincinnati Children's Group [64] reported that 52% of EoE cases had

normal esophagram. Abnormal findings were irregular contractions (15%), strictures (10%), rings (6%), mucosal irregularities (5%), and small caliber esophagus (4%).

Allergy Testing

Although the pathogenesis of EoE is not predominantly IgE-mediated, several studies showed positivity of allergy testing that may be related to EoE or to other associated atopic disease [20, 51, 66–68]. EoE is more commonly associated with positive skin prick test (SPT) or serum-specific IgE (sIgE) to foods than to aeroallergens [51, 69, 70].

Serum food-specific IgE was noted in 82% of an adult group [51] and in 59% of a pediatric group [68]. In a pediatric study, the positivity of serum sIgE testing was 42% in patients who had negative SPT [68].

SPT was positive in 73% of pediatric patients [69] and in 50% in adults [70].

In children, the most common causative food was milk, often in combination with one or more other foods [66].

In a study on 319 pediatric patients, the diagnostic value of SPT in identifying the causative food showed 82–97% specificity and 18–88% sensitivity; the PPV ranged from 26 to 96%, with an average of 47%. In the same study, allergy patch testing with foods showed PPV of 12–86% (average 44%) and NPV of 31–99% (average 90%), which support a role of cell-mediated mechanism in EoE. The combination of SPT and APT slightly increased the PPV for some foods [66, 67]. The inconsistency in reported findings on APT and the lack of standardized material limit its use in practice.

Patients with EoE also have higher rates of aeroallergens sensitization than the general population. Aeroallergen positivity was reported in 44–86% by serum-specific IgE testing and in 71–93% by SPT [20]. It is hard to make a cause-and-effect relationship unless there is relevant seasonal symptom exacerbation.

Emerging Diagnostic Tools

Patients with EoE may undergo frequent endoscopies, which require sedation or general anesthesia with concern about subsequent negative effect on cognitive development in children [71]. Hence, less invasive procedures are being developed, with initial promising results and may reach their application in practice in the near future.

Transnasal esophagoscopy was evaluated by Friedlander et al. [72] by using a bronchoscope for transnasal esophagoscopy without sedation on children while they were distracted by using three-dimensional movie goggles. Compared to conventional esophagogastroduodenoscopy (EGD) procedure, the obtained biopsies were as good and the parents and patients had a higher degree of preference. Furthermore, there was a 62% reduction in total cost. Such a

procedure would be especially useful for documenting an objective evidence for the result of multiple food challenges.

Cytosponge is a procedure originally developed for evaluating Barrett's esophagus. It involves a histology-collection spherical mesh inside a gelatin capsule attached to a string. Five minutes after the patient has swallowed the capsule into the stomach, the capsule dissolves and the cytosponge is pulled up, scraping the esophageal mucosa for cytology examination in lieu of excision biopsy. In a small feasibility study, Katzka et al. [73] assess the utility of this device in EoE compared to standard endoscopic biopsy. Cytosponge showed 85% sensitivity and 56% specificity in detecting > 15 eosinophils/hpf compared to standard biopsy.

Enterotest is an endoluminal string device that has been originally used for identifying enteric pathogens. It was used by Furuta et al. [74] to assess EoE disease activity by measuring several extracellular eosinophil secondary-granule proteins such as major basic protein-1, eosinophil peroxidase, eosinophil-derived neurotoxin, eosinophil cationic protein, and Charcot-Leyden crystal protein/galectin-10. It showed a significant correlation with the findings in conventional biopsy, including the eosinophil count.

Functional luminal imaging probe (EndoFLIP®) uses high-resolution impedance planimetry to measure esophageal distensibility and compliance in a cross-sectional area. It was used in one study on patients with EoE and demonstrated a significant decrease in esophageal distensibility and compliance compared to control subjects [75]. Another study showed that a decrease in esophageal distensibility is associated with an increased risk of food impaction and the need for esophageal dilation [76]. However, neither of these two studies showed a correlation between the histologic eosinophilic density and the esophageal distensibility or compliance. Chen et al. reported a moderate correlation between the severity of the endoscopic ring score and the distensibility plateau, which could serve as an indicator of tissue remodeling [77]. A major limitation of this procedure is that it does not differentiate between a true narrowing of the esophagus and a transient distension-mediated contraction. This problem might be overcome by an update in the software [78].

Differential Diagnosis

Since the clinical symptoms of EoE are not pathognomonic and sometimes the biopsy findings are inconclusive, it would be prudent to rule out other GI disorders.

Gastroesophageal Reflux Disease

GERD is a common GI disorder of any age. Its symptoms vary from heartburn and regurgitation to chronic esophageal inflammation. In addition to pH monitoring, a biopsy usually

reveals basal cell hyperplasia, intracellular edema, dilated intercellular spaces, lengthening of the lamina propria papillae, and intraepithelial eosinophils usually $< 15/\text{hpf}$ [79, 80].

Most cases of EoE were initially diagnosed as GERD and were managed accordingly. Both conditions may coexist, either the reflux is secondary to EoE or GERD predisposes to the pathogenesis of EoE. Acid-peptic damage of the esophageal mucosa exposes deep layers of the epithelium to antigens and leads to the development of EoE [81]. Acid exposure also induces the expression of VCAM-1, an adhesion molecule that is recognized by eosinophil cell surface and facilitates eosinophilic inflammation [82].

PPI-Responsive Esophageal Eosinophilia

PPI-REE is a term to describe patients with clinical characteristics similar to EoE and high counts of esophageal eosinophilia who respond well both clinically and histologically to PPI therapy [81]. It was first described in 2006 [83] in a series of pediatric patients and accounts for 40% of children [84] and 30–50% of adults [85, 86] with esophageal eosinophilia. There are no clinical, endoscopic, histological, or molecular markers that can distinguish between EoE and PPI-REE [81, 86]. Therefore, patients with esophageal eosinophilia $> 15/\text{hpf}$ should have an 8-week trial with high-dose PPI before being diagnosed as EoE [20]. Transcriptome analysis revealed that PPI-REE is a disease entity with significant overlapping molecular signature with EoE and may be a sub-phenotype of EoE [5].

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is a group of chronic gastrointestinal disorders resulting from an inappropriate inflammatory response to gut microbiome in genetically susceptible individuals. Crohn disease affects the entire thickness of the wall of the GI tract anywhere from the mouth to the anus, typically in a discontinuous manner. On the other hand, ulcerative colitis is limited to the colonic mucosa starting from the rectum in an uninterrupted pattern all the way to the cecum [87].

Histologically, the architectural disarray is accompanied by a dense inflammatory infiltrate characterized by plasma cells, lymphocytes, neutrophils, eosinophils, macrophages, and mast cells [88]. The role of eosinophils in the pathogenesis of IBD is an ongoing area of research [89–92]. Although intestinal eosinophilia can be present, their role varies based on disease activity [93]. Plasma cell clustering in the lamina propria is one of the earliest histologic features of IBD [94].

Esophageal Crohn disease is rare and typically presents in patients with ileocolonic Crohn. It can be asymptomatic in 33% of patients, but it can present with non-specific symptoms such as chest pain, dysphagia to solids, odynophagia,

vague abdominal pain/dyspepsia, nausea, and vomiting. Like any other part of the gastrointestinal tract, the esophagus can show inflammation, stricture, or fistula formation [95]. Crohn-related esophageal eosinophilia presents with clinical symptoms similar to EoE but will have less inter-epithelial edema and basal hyperplasia and is driven by a Th1 stimulus; meanwhile, EoE is mostly Th2-driven [96].

Connective Tissue Disorders

A recent retrospective analysis revealed an 8-fold increased risk of EoE in patients with connective tissue disorders (CTDs), including Marfan syndrome, hypermobile Ehlers-Danlos syndrome, and joint hypermobility syndrome (relative risk 8.1) compared with the general population. It was also found that there are a higher percentage of patients with CTDs in the EoE population [97].

Some authors reported 42 patients with EoE in association with features of CTDs and coined the term “EoE-CTD.” These patients had lower BMI and tend to have an increased risk for extraesophageal eosinophilic gastrointestinal disease [97].

Infectious Esophagitis

Though infectious esophagitis can occur in patients with normal immune function [98], subjects with primary or secondary immunodeficiency as well as those with abnormal structure/function of the esophagus are at a higher risk [99]. *Candida* is the most common cause of fungal esophagitis. The endoscopic appearance shows white plaques covering the mucosa resembling cottage cheese. Mucosa can also have superficial and deep ulceration, friability, and strictures. Herpetic esophagitis can result from reactivation of a latent infection, particularly in patients with HIV or who underwent solid organ or bone marrow transplants. The endoscopic appearance ranges from small vesicles to various degrees of ulcerations, and the mucosa can be covered with pseudo-membranes or exudates [98].

The clinical presentation can be in the form of various degrees of dysphagia, odynophagia, retrosternal chest pain, and fever. Endoscopy and microbiologic cultures would be diagnostic.

Natural Course and Complications

For the most part, EoE is a chronic and relapsing condition, which may result in progression from inflammation to irreversible fibrostenosis [100, 101]. Although children may suffer failure to thrive, rarely, there are nutritional consequences in adults, and the disease remains localized to the esophagus [102].

In a retrospective review of data on 57 children with EoE followed for 7.6 years, EoE had resolved in 14%, resolved then relapsed in 53%, and persisted in 33% [103]. Relapse is common in EoE. In another study on 30 adults followed for 11.5 years, persistence of clinical symptoms and histological findings were noted in most of the patients [102].

Long-standing chronic inflammation in EoE often leads to irreversible remodeling of the esophagus in the form of narrowing or stricture formation. Food impaction is the most common complication and can be the initial presentation or during the course of the disease [33, 104]. In one series, strictures were noted in 31% of adults compared to 6% in children [104]. Long-segment esophageal narrowing can be present as multiple concentric rings or small caliber esophagus and has been reported in up to 10% of adult patients. The degree of the stenosis may vary and can involve the full length of the esophagus in long-standing, severe cases [20]. EoE disease does not seem to limit the life span and is not associated with high cancer risk [105].

Esophageal rupture may occur secondary to retching and vomiting during an episode of food impaction or during endoscopy or dilatation [106] and can be in the form of intramural tear or full perforation (Boerhaave syndrome) [43]. Leakage of gastric contents in the chest cavity requires urgent surgical intervention.

Conclusion

EoE is a chronic immune-mediated disease with predominant eosinophilic inflammation and symptoms related to esophageal dysfunction. Its estimated overall prevalence is 22.7 cases per 100,000 population and is seemingly increasing, at least partly due to better recognition. Although its pathogenesis is not completely understood, there is a role for food allergens in its etiology though is not identified in every patient. The clinical presentation varies with age and the patient's ability to communicate symptoms. Children may have a wide variety of non-specific symptoms due to esophageal motility dysfunction. Most common manifestations in infants are feeding difficulties with failure to thrive. Adolescents and adults are more likely to present with dysphagia to solid foods and may escalate to food impaction. Spontaneous esophageal rupture from forceful retching is a rare but serious complication.

The diagnosis is suspected by the symptoms, lack of adequate response to a trial of PPI therapy, endoscopic features, and biopsy findings of > 15 eosinophils in any high-power field. Biopsy should be obtained even when the mucosa visually appears normal. A role of food allergen may be suspected by the medical history, dietary elimination trials, or allergy testing, but confirmation requires documentation of improvement on avoidance and recurrence after reintroduction of the suspected food(s).

Since the clinical symptoms of EoE are not pathognomonic and sometimes the biopsy findings are inconclusive, it would be prudent to rule out other GI disorder, including GERD, PPI-responsive esophageal eosinophilia, IBD, connective tissue disorders, and infectious esophagitis.

Diagnostic guidelines were first developed in 2007 and are periodically updated. The guidelines by the American College of Gastroenterology in 2013 emphasized the importance of excluding secondary causes of mucosal eosinophilia and documenting response to treatment (dietary elimination and/or topical steroids). Long-standing chronic inflammation in EoE can lead to fibrosis and irreversible remodeling of the form of narrowing or stricture formation. Esophageal rupture may occur secondary to retching or vomiting during an episode of food impaction. Towards enhancing a comprehensive diagnostic evaluation, recent studies promise of certain emerging procedures, such as transnasal esophagoscopy, cytosponge, enterotest, and functional luminal imaging probe.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval Not applicable; this is a review article.

Informed Consent Not applicable; this is a review article.

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