

Eosinophilic esophagitis: an immune-mediated esophageal disease

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Published online: 12 April 2013
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Abstract Eosinophilic esophagitis (EoE) is an emerging disease defined by esophageal dysfunction, by typical endoscopic findings and by abnormal eosinophilic inflammation within the esophagus. Eosinophilic accumulation in the esophagus occurs as a result of esophageal overexpression of pro-inflammatory mediators, including T cells and mast cells, cytokines such as interleukin (IL)-13, IL-5 and IL-15, as well as chemoattractants (eotaxin and transforming growth factor- β 1, fibroblast growth factor and the newly characterized gene—thymic stromal lymphopoietin, which is a key regulator of allergic sensitization initiation). The role of allergy, particularly food allergy in EoE is indisputable, as elimination diet is a proven commonly used treatment for the disease. However, unlike classical immediate IgE-mediated reaction to allergen, EoE is associated with an altered immune response, characterized by a combination of IgE-mediated and non-IgE-mediated mechanisms. In this review, we aim to discuss the many typical aspects of EoE as opposed to other entities involving the esophagus, with focusing on the aberrant immune-mediated key players contributing to the pathogenesis of this unique disease.

Keywords Esophagitis · Eosinophilic inflammation · Mix IgE and non-IgE mediated · Food allergy · Elimination diet · Eotaxin-3

Introduction

The finding of esophageal eosinophils denotes pathology since the esophagus, unlike all other segments of the gastrointestinal tract, normally lacks eosinophils [1].

However, the presence of esophageal eosinophils is not specific for a particular disorder because eosinophil accumulation in the injury or inflammatory response of the esophagus occurs in a variety of states, including gastro-esophageal reflux disease (GERD), chronic esophagitis, parasitic and fungal infections, inflammatory bowel disease, celiac disease, hypereosinophilic syndrome, scleroderma, drug and/or iatrogenic-induced states such as caustic injury and in Graft-versus-host disease following transplantation [1]. The diagnosis of eosinophilic esophagitis (EoE) requires characteristic clinical, endoscopic and pathologic findings that can only be obtained at endoscopy, as well as elimination of other causes of esophagitis, especially GERD [2]. In an effort to standardize the diagnostic approach to EoE, consensus guidelines were published in 2007 that define EoE as a clinicohistopathologic disorder requiring the presence of 15 eosinophils/high-powered field (hpf) or greater on esophageal biopsy and the exclusion of GERD or proton-pump inhibitor

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(PPI)-responsive esophageal eosinophilia based on a trial of high-dose PPI therapy or a negative pH probe [2]. Multiple new criteria have been proposed including pathological criteria such as clusters of eosinophilic abscesses or clinical criteria such as response to dietary elimination [3–5].

Symptoms, dysregulation of esophageal gene expression and pathology are largely reversible following reduced exposure to specific food antigens as well as anti-inflammatory therapy, but chronic treatment is necessary to prevent relapse [5–8]. Therefore, eosinophilic esophagitis is a disease with unique features that include chronic esophagitis, atopy, immune sensitization to oral antigens, reversibility and familial association.

Clinical presentation and epidemiology of EoE

Eosinophilic esophagitis can be diagnosed at any age. Clinical characteristics are not specific and vary by age groups, and younger patients more commonly have non-specific symptoms than older children. Infants usually present with irritability, feedings refusal, vomiting and failure to thrive, whereas older children and young adults typically present with dysphagia, vomiting, heartburn and episodic food impaction [9–13]. In fact, in adult series, 50 % of patients requiring endoscopic intervention for food impaction are subsequently diagnosed with EoE and 40 % of patients with EoE report previous multiple episodes of food impaction [14, 15]. More subtle symptoms are occasionally reported such as slow eating and chewing, avoidance of specific solid foods such as rice, meat and bread and drinking water to assist swallowing during meals as an adaptive behavior to esophageal dysfunction.

There are no typical findings on physical examination suggesting the diagnosis of EoE, although failure to thrive and signs of atopy may be present.

The condition affects males more commonly with a 3:1 male-to-female ratio and typically affects Caucasians [16, 17].

The incidence of EoE has raised in the last decade with rates of up to 35-fold increase reported [18–20]. Data on the incidence and prevalence of adult EoE have come almost exclusively from the USA and Switzerland. Straumann et al. reported that the estimated annual incidence of EoE in adults in Switzerland in 2011 has climbed up to 2.45 per 100,000 [21]. At the same study, the prevalence of this disease in adults increased up to 42.8 patients per 100,000 inhabitants [21]. For pediatric EoE, the reported figures are higher, Noel et al. reported during the period between 2000 and 2003, the calculated incidence in pediatric population was 10 per 100,000, while the prevalence among children for the same period was estimated to be 42.9 per 100,000 [22]. The epidemiological figures vary

widely in the different studies. These differences can be attributed to methodology, environmental and/or genetic factors. The reason for this ascension is multifactorial, with both increased awareness of clinicians, and availability of gastroscopic procedures and increased incidence of overall atopic conditions playing a role [23, 24].

There is evidence that EoE has a strong familial association [22, 25–28], as nearly 10 % of parents of patients with EoE have a history of esophageal strictures and approximately 8 % have biopsy-proven EoE [29]. Rotenberg et al. reported 26 multiplex families with EoE and demonstrated conserved clinical, pathologic, and genetic features compared with patients with a sporadic EoE [20]. The estimated sibling risk recurrence ratio (RR) for EoE is approximately 80 [1]. This value is markedly higher compared with that of siblings with other atopic diseases with familial inheritance patterns, such as asthma (RR = ~2) [30].

Diagnosis of EoE

Eosinophilic esophagitis is a clinicopathological condition, and as such, an endoscopy with mucosal esophageal biopsies must be done in order to establish the diagnosis.

Typical endoscopic features, although not pathognomonic, are mucosal furrowing, trachealization (macroscopic fixed esophageal rings), mucosal friability, white exudates (representing microscopic eosinophilic abscesses) and luminal strictures [31]. These features can be found along the entire length of the esophagus as opposed to reflux esophagitis, in which findings are usually confined to the distal esophagus. Almost 10 % of normally appearing endoscopes in patients referred for dysphagia had histologic evidence of EoE, and in those with macroscopic findings suggestive of EoE, only 38 % had histologic evidence of EoE [31]. Two to four biopsies should be taken from the proximal and distal esophagus. Sensitivity increases, respectively, to 84, 97 and 100 % if 2, 3 or 6 biopsies specimens are taken [32]. Gastric antrum and duodenal biopsies should also be taken in order to rule out other causes of esophageal eosinophilia. The pathologist should report all abnormalities associated with EoE, such as the peak eosinophil value (obtained from the area with the highest density of eosinophils), eosinophilic microabscesses, surface layering of eosinophils, extracellular eosinophil granules, basal cell hyperplasia, dilated intercellular spaces and lamina propria fibrosis [2].

Current guidelines for histologic diagnosis of EoE state that presence of 15 eosinophils or more per hpf in the most affected sample is diagnostic of EoE [2]. Inflammatory changes might be focal or patchy and may not involve all biopsies uniformly. The normal esophagus lacks tissue

eosinophils although other pathologies such as GERD are also associated with presence of tissue eosinophilia. Moreover, it must be considered that 39–75 % of patients with 15 or more eosinophils per hpf have resolution of tissue eosinophilia with PPI treatment; therefore, it is imperative to treat such patients with PPIs for a period of 8–12 weeks before establishing the diagnosis of EoE [33, 34]. The presence of eosinophilic microabscess and surface layering of eosinophils is more suggestive of EoE [3, 4]. Other findings described are increased extracellular staining of esophageal granules and granule proteins (such as major basic protein, eosinophil peroxidase and neurotoxin), increased number of mast cells and increased tryptase staining compared to biopsies from GERD or normal adults [29, 35]. Presence of lamina propria fibrosis in the process of tissue remodeling which is responsive to treatment with steroids and anti-IL-5 antibodies suggests a central role of fibrosis in the pathogenesis of symptoms such as dysphagia [3, 36, 37]. The association between esophageal inflammatory burden and symptom severity is controversial both at diagnosis and for follow-up of treatment success [31, 38–41]. Occasionally, patients are evaluated for presence of GERD by pH monitoring, which is typically normal, although recently a subset of patients has been described with PPI-responsive esophageal eosinophilia, in which gastroesophageal reflux had been ruled out by conventional diagnostic tools [2].

Endoscopic ultrasonography is a novel diagnostic modality for assessment of esophageal dysfunction, investigated recently. Since the longitudinal (and not the circular) muscle contraction is markedly diminished in EoE patients, changes in the muscle thickness (a marker of longitudinal muscle contraction) are markedly diminished in these patients [42].

It is important to emphasize that histopathologic features must be interpreted in conjunction with the clinical information of the patient.

Atopy and EoE

Numerous murine models and clinical studies have shown strong association between EoE and atopy [2, 43–48], including food allergies, atopic dermatitis, asthma, allergic rhinitis and allergic conjunctivitis [10, 48–51]. The majority of patients with EoE (50–60 %) have prior history of atopy [52, 53], and 28–86 % of adults and 40–93 % of pediatric EoE have another allergic disease [7, 44, 46, 52–54]. Only 15–43 % of EoE patients have IgE-mediated hypersensitivity, as defined by a positive skin prick test (SPT), radioallergosorbent test (RAST), increased serum levels of eosinophils, a positive atopy patch test (APT), as well as clinical and histological response to an elemental

diet [5, 10, 29, 47, 52, 55, 56]. Although none of these studies documented clinical significance of serum IgE sensitization to EoE diagnosis or management, elevated specific food antibodies measurements by RAST in EoE patients were documented in a few articles [3, 46, 54]. The combination of SPT with APT increases the yield of diagnosis to 70 % [5]. Positivity of the three modalities—SPT, RAST and APT—has identified milk, eggs and wheat as the most common allergens. SPT and patch test additionally found corn, beef, chicken, barley, oat and rice most commonly [30]. Although only a minority of EoE patients (10–15 %) have a history of food anaphylaxis [46, 51, 57], a thorough allergic workup is indicated in all EoE patients, including SPT or RAST for immediate-type food allergy, to identify allergic patients with the risk of anaphylaxis [2, 5, 56].

Yet, not every patient's clinical course suggests a causative food allergen [51]. This fact raised the hypothesis that alternative triggers to EoE such as aero and epicutaneous allergens exist. This hypothesis was supported with an experimental model of EoE, in which mice had repeated intranasal exposure to the respiratory aeroallergen *Aspergillus fumigatus*, which induced both airway and esophageal eosinophilic inflammation [58]. Additional support to the role of aeroallergens as a trigger for EoE is the seasonal variation in presentation, with greatest incidence in late summer and fall [29, 52, 53]. Together, these findings provide evidence that development of murine esophageal eosinophilia relies on a close relationship between the mucosal immune systems of the esophagus, lung and skin [59].

Pathogenesis of EoE

Unlike classical immediate IgE-mediated reaction to allergen, EoE is associated with an altered immune response, characterized by a combination of IgE-mediated and non-IgE-mediated Th2 mechanisms [60–63]. Eosinophilic accumulation in the esophagus occurs as a result of esophageal overexpression of pro-inflammatory mediators including lymphocyte subpopulations, predominantly T cells, as well as IgE, and *FcεRI*-positive cells such as mast cell, cytokines (IL-13, IL-5 and IL-15) and chemoattractants (eotaxin and *TGF-β1*) and fibroblast growth factor (*FGF*) [61, 63–65]. The evidence for the significant role of T lymphocytes in EoE was established by failure to develop antigen-induced EoE in B cell-intact mice, which were T cell-deficient [60].

In this paragraph we will discuss the most important players in the pathogenesis of EoE.

Eosinophil is a multifunctional pro-inflammatory leukocyte implicated in the pathogenesis of numerous

inflammatory processes [29, 66]. This cell modulates multiple aspects of the immune response, by producing a wide range of inflammatory cytokines (including IL-1, IL-3, IL-4, IL-5, IL-13), chemokines (eotaxin), granulocyte–monocyte colony-stimulating factor (GM-CSF), *TGF- α* , *TGF- β* and tumor necrosis factor (*TNF*) α [55, 67], and by a release of granule components, which are toxic to a variety of tissues, including intestinal epithelium [68–70]. These granules contain a crystalloid core, composed of cationic proteins with numerous pro-inflammatory properties [71]. For example, major basic protein (MBP), eosinophil peroxidase (EPO), and eosinophil cationic protein (ECP) have cytotoxic effects on epithelium in concentrations similar to those found in biological fluids from patients with eosinophilia [22, 55, 59, 69, 70].

Eosinophil recruitment into inflammatory tissue is a complex process regulated by multiple inflammatory mediators as previously discussed [72–74]. However, in allergic diseases, eosinophil trafficking into inflammatory tissue, selectively regulated by IL-5 and eotaxin [75, 76]

IL-5 is a specific eosinophil differentiation, growth, activation and survival factor, generated predominantly by Th2 cells, but also by eosinophils and by mast cells in chronic allergic reactions [76]. This cytokine may induce eosinophil trafficking to the esophagus either by enhancing eosinophil responsiveness to endogenous chemokines expressed in the esophagus, such as eotaxin, or by up-regulating homing receptors specifically involved in eosinophil trafficking to the esophagus [76]. *IL-5* is over-expressed in esophageal epithelial biopsy specimens, and its central role in EoE pathogenesis has been established in numerous studies [61, 76, 77]. First, studies demonstrated that EoE is an *IL-5*-dependent disease in which use of *IL-5* null or anti-*IL-5*-treated mice correlated with a marked reduction in esophageal eosinophilia [76]. In addition, *IL-5*-mediated eosinophilia promotes esophageal tissue remodeling, a histological finding supported by several clinical reports [77]. A thickened basal layer and collagen accumulation were observed in the lamina propria of esophageal tissue sections of CD2–*IL-5* transgenic mice, findings which were absent in *IL-5* gene–deficient allergen-challenged mice [77].

Eotaxin is an eosinophil-selective CC chemokine, constitutively expressed in the gastrointestinal tract, and is critical for the maintenance of eosinophils in this tissue [59, 78–80]. Its biological activity is enhanced by *IL-5*, which increases the circulating pool of eosinophils and primes eosinophils to have enhanced responsiveness to eotaxin [59, 78, 81]. The critical role of eotaxin allergen-induced eosinophilic infiltration in the gastrointestinal tract was demonstrated in eotaxin-deficient *IL-5* transgenic mice, which showed markedly impaired esophageal eosinophilia, compared with eotaxin intact *IL-5* transgenic

mice [82]. This finding indicates the cooperation of eotaxin with other eosinophil-active chemoattractants in the regulation of eosinophil trafficking to the esophagus [72, 74]. Further support for the importance of this pathway to EoE was observed in mice harboring a genetic deletion in the eotaxin receptor [CC chemokine receptor 3 (CCR3)] who were protected from development of EoE [83]. Among the eotaxins, the eotaxin-3 (in contrast to eotaxin 1 or eotaxin 2) is specifically overexpressed in EoE [1, 83]. Indeed, genetic studies demonstrated that eotaxin-3 gene is the most highly induced gene in EoE. Furthermore, it was found that the levels of this chemokine expression in the esophagus strongly correlated with disease severity based on basal layer expansion and levels of eosinophils and mast cells [83].

IL-13 is Th2 cytokine that appears to be a particularly important player in eosinophil trafficking into the esophagus, as demonstrated in numerous murine models. One model showed that intratracheal *IL-13* delivery induces EoE, a finding that was blocked with anti-human *IL-13* antibody and found to be diminished in *IL-13*-deficient mice [84, 85]. This finding strongly implicates an important role of respiratory immune responses in the etiology of experimental EoE [85]. In the same study, the essential role of *IL-5* in *IL-13*-induced EoE was established by failure to induce EoE in *IL-5* gene targeted mice exposed to intratracheal *IL-13*, while wild-type control mice developed marked EoE [85]. Another important finding of this study was that *IL-13*-induced EoE occurs by a signal transduction and transcription 6 (STAT6)-dependent mechanism, as mice with a targeted deletion of STAT6 failed to develop allergen- and *IL-13*-induced experimental EoE [85]. *IL-13* is a critical signaling molecule that can upregulate genes expression of the EoE transcriptome and increase eotaxin-3 expression on esophageal epithelial cells [86]. This cytokine also promotes fibrosis, angiogenesis and epithelial hyperplasia, which contribute to esophageal remodeling seen in this disease [87].

Mast cell Several clinical and experimental murine studies have shown mast cell accumulation and degranulation of mast cells in the esophagus of EoE patients [61, 64, 88].

Since this cell stores and produces an abundant number of potent inflammatory mediators, including cytokines that activate eosinophils and molecules that directly promote tissue remodeling [70], mast cells may be particularly important in disease pathogenesis [89, 90]. In addition, mast cells express CCR3 and respond to CCR3 ligands [77, 78, 92], similarly to eosinophils. Thus, eotaxin-3 may also target mast cells in EoE. It has been found that the level of mast cells also correlated with disease severity based on eosinophil counts and the degree of epithelial basal layer expansion [83].

TGF β 1 is a pro-fibrotic molecule produced by epithelial cells and inflammatory cells, including eosinophils and mast cells. This molecule is overexpressed in EoE and plays an important role in the esophageal remodeling [65]. It has been found that eosinophilia positively correlates with the degree of expression of *TGF- β 1* [91, 93, 94]. Since only some patients with EoE develop esophageal strictures, a subset with EoE may have a genetic predisposition to stricture formation [65].

Fibroblast growth factor (FGF) is an essential protein involved in normal cell development, cell differentiation and tissue repair after injury [95, 97]. It is released by a wide variety of cells, including the eosinophils. *β -FGF* has been shown to enhance the half-life of cells and could possibly increase the overall lifetime of the eosinophil in the esophagus [97]. It is also a pro-fibrotic cytokine that may promote both fibrosis and angiogenesis by binding to the extracellular matrix. Plasma as well as local FGF expression was found to be increased in EoE patients compared with healthy control and GERD subjects [97].

IL-15 induces CD4+ T-cell proliferation and Th2 cytokine production as well as eosinophil-specific chemokine mRNA expression by primary esophageal epithelial cells, which provides a mechanistic functional pathway for IL-15 in EoE [96, 97]. The esophageal biopsy specimens from patients with EoE and the esophagus of mice with experimental EoE have increased expression of IL-15 mRNA and protein [98]. Importantly, mice deficient in the IL-15R gene are protected from the development of experimental EoE. Induced IL-15 expression significantly correlates with esophageal eosinophilia in humans, and IL-15 levels were reduced following treatment in patients with improved EoE [98].

Genetics of EoE

Whole genome-wide expression analysis identified a striking EoE transcript signature, involving approximately 1 % of the human genome [83]. This EoE transcriptome comprises altered expression of approximately 574 genes and is highly conserved across patient phenotypes, regardless of sex, age and allergic status [83, 99]. A comparison of transcriptomes of patients with allergic and non-allergic EoE revealed that the gene expression signature is conserved between these 2 major phenotypes [83], indicating a common pathway for both phenotypes, regardless of what factors primarily activated the inflammation [1, 100].

The most highly expressed gene in the esophagus of EoE patients is eotaxin-3 (a 53-fold increase compared with healthy individuals) [83, 99]. A single nucleotide polymorphism (SNP) in this gene (+2496T > G,

rs2302009) was found to be associated with EoE, using population-based case-control and family-based transmission disequilibrium analyses, but the disease-associated allele is only present in 14 % of patients [83]. Clearly, other genes are involved in EoE risk, phenotype and patient outcome [100].

In contrast, other genes, like filaggrin (*FLG*), a skin structural barrier protein, are downregulated in this disease. In various cutaneous disorders including atopic dermatitis, which frequently occur with EoE, the loss-of-function mutation in *FLG* leads to subsequent defects in epidermal barrier function [100–102]. Interestingly, the *FLG* association appeared to be independent of the presence of atopic dermatitis in patients with EoE, suggesting an alternative function for *FLG* in regulating the epithelial structure within the human esophagus [101].

It has been found that IL-13 is specifically upregulated in the esophagus of patients with EoE and might function as a master regulator of the EoE transcriptome [86]. Among the genes upregulated by this cytokines is periostin, an extracellular matrix protein functions as an adhesion molecule of eosinophils recruited to the esophagus by eotaxin-3 [14]. This molecule induced is also induced by *TGF β* and markedly overexpressed in EoE esophagus. Notably, levels of periostin strongly correlated with esophageal eosinophil levels [14].

In addition, it has an important role in promoting fibrosis which is seen in EoE. It was also found that steroid therapy induces disease remission and effectively normalizes as much as 98 % of the EoE transcriptome, including eotaxin-3 [86, 99]. Nevertheless, a set of epithelial differentiation regulation, homeostasis and pathogenic responses genes has been shown to remain abnormal and might be important in predisposing to disease relapse [2]. Interestingly, a specific esophageal transcriptome that was identified based on mast cell levels only partially overlaps with the transcriptome defined by eosinophil levels alone, indicating that mast cells and eosinophils are likely independently involved, at least in part in the pathogenesis of the disease [83, 90, 99].

Recently, a genome-wide analysis has identified the first EoE susceptibility locus at 5q22 [102], with two genes located in the susceptibility haplotype include thymic stromal lymphopoietin (*TSLP*) and (*WDR36*). Among these two, *TSLP* was found to be the stronger candidate gene because of its overexpression in the esophagus of patients with EoE and its known biological activity as a key regulator of allergic sensitization initiation [104]. Taken together, it is rational to hypothesize that the increased *TSLP* expression leads to increased allergen sensitization and to development of EoE [103, 105]. The specificity of the *TSLP* genetic association with EoE was demonstrated in a broad analysis of genetic variants within 53 candidate

genes involved in allergic responses, immune responses or both [103]. Another interesting finding of this analysis was a genetic variant in the *TSLP* receptor gene located on a pseudoautosomal region of the X-chromosome, which was also linked with EoE susceptibility in male patients. This finding may provide an explanation for the contribution of *TSLP* mechanism to male predominance seen in EoE [103].

The clinical use of specific biological markers and genotypes to predict EoE diagnosis, prognosis or both is not yet ready for clinical application. However, esophageal gene expression is likely to emerge as a key molecular biomarker that helps differentiate EoE from other states such as GERD and to distinguish glucocorticoid-responding versus non-responding disease states [2, 78].

Natural course of EoE

The natural course of EoE is chronicity, with complications of esophageal thickening progressing over time in untreated patients. The minority of patients are observed to develop tolerance to food allergies or spontaneously resolve eosinophilia and clinical symptoms such as dysphagia [106]. On the other hand, EoE does not seem to progress into more generalized disorder of the gastrointestinal tract such as eosinophilic gastroenteritis or inflammatory bowel disease, and no association with esophageal adenocarcinoma has been observed [30, 106–108].

Treatment for EoE

The goals of treatment are control of symptoms, prevention of complications and reversal of complications such as esophageal fibrosis [8]. It is currently debatable which treatment strategy should be employed in the symptomatic patient: Should histologic remission be the goal of treatment or whether clinical improvement guides the treatment approach. Being a chronic condition, it is also unclear what should the long-term goals be and what is the proper follow-up modality. Moreover, a significant and unknown proportion of patients are asymptomatic at diagnosis, and currently, the treatment approach to these patients is unknown [109].

Dietary manipulation is the cornerstone of treatment as food allergy is extremely common in EoE patients. Three central approaches are currently employed by most clinicians which have been proven to be effective: dietary restriction based on allergy testing, dietary restriction in United States based on elimination of the 6 most likely food antigens allergens (cow's milk, soy, wheat, eggs, seafood and tree nuts) and employing an elemental diet

(amino acid based formula administered either orally or by nasogastric tube). The elemental diet approach has been shown to be an effective treatment in up to 97 % of patients although adherence to therapy and cost of elemental formula are a major issue with this approach [30]. Elimination diet based on positive allergy testing has been shown to be effective treatment in 77 % of patients, whereas the 6 food elimination diet was effective in 74 % [7]. Retrospective studies comparing these approaches have shown the elemental dietary approach to be superior. A repeat endoscopy might be indicated in cases which the specific allergen has not been identified [110, 111]. It is recommended that the offending allergen be eliminated indefinitely and the patient should be referred to a dietitian for education and to assure that the patient is receiving the proper protein, calories, trace elements and vitamins.

Proton-pump inhibitors

Classically, PPIs have had a role in distinguishing GERD from EoE, in treating combined GERD and EoE and for symptomatic relief. It has been considered to have no role in treating proved EoE cases. Recently, a subset of PPI-responsive esophageal eosinophilia has been described, and it is currently unknown whether they actually represent a subcategory of EoE. Potential explanations for the role of the PPIs in the disease include healing of a disrupted epithelial barrier to prevent further immune activation, decreased eosinophil longevity, inherent anti-inflammatory properties of PPIs or unreliable diagnostic testing. Current guidelines therefore suggest a trial of 8–12 weeks of PPI in selected cases [2].

Topical steroids

Topical steroids are currently the mainstay of treatment for EoE. They have been shown to induce both clinical and histological remission and have been associated with reversal of tissue fibrosis. Swallowed fluticasone propionate, in varying doses, was shown to induce histologic response and symptom resolution in up to 94 % after 4 weeks of treatment in several prospective pediatric studies [90, 113]. Another study comparing dietary therapy to swallowed fluticasone found fluticasone to be more effective [7, 100]. Oral viscous budesonide (budesonide suspension mixed with sucralose) was associated with 87 % histologic resolution. Another study using swallowed nebulized budesonide showed complete resolution in 72 % [7, 29].

Two limitations to oral swallowed steroids exist: dependency on treatment and oral fungal infections. Following discontinuation of 6 weeks treatment trial, almost

all patients reported recurrence of EoE symptoms within an average of 9 months [6]. Oral thrush was reported in up to 16.7 % in patients treated with either fluticasone or budesonide [37, 112]. No systemic side effects have been reported with this regimen.

Oral systemic steroids

An early study demonstrated oral steroids to be effective in histological resolution of EoE [114]. A more recent pediatric study comparing oral systemic steroids (prednisone) to oral topical swallowed steroids (fluticasone) found similar efficacy for both regimens despite better histological effect with prednisone but fewer systemic side effects with fluticasone [112]. As such, oral steroids are reserved for extreme cases such as severe failure to thrive or significant stricture unresponsive to local treatment.

Leukotriene receptor antagonist

Montelukast—a leukotriene D receptor antagonist—has a role in the process of eosinophil function but not in eosinophil recruitment. An adult trial has shown clinical but no histological improvement. High doses were required with associated side effects and early flares after dose reduction [115]. According to the current guidelines, this treatment is not recommended for EoE, since the lack of combined clinical and histologic benefit and potential side effects currently outweigh any potential benefit [2].

Anti-IL-5 antibody

Interleukin (IL)-5 has a central role in eosinophil proliferation and activation and has been shown to be overexpressed in patients with EoE. Preliminary clinical studies have shown that administration of mepolizumab, a humanized monoclonal antibody against IL-5, not only reduces EoE symptoms to variable extent, but also reduces eosinophil load in the blood and in the tissue and decreases eosinophil activation [81, 116–118].

Reslizumab [120] is another humanized antibody against IL-5, when it was examined on EoE patients and a placebo group, although reduction in esophageal eosinophilic load was achieved in the EoE patients group, symptoms improvement was observed in both the treatment and the placebo groups, with no significant difference.

Other potential pharmacological agents such as anti-IL-13 and anti-eotaxin are currently being investigated.

Esophageal dilation

Dilation of esophageal strictures is effective for relieving dysphagia, but has no effect on underlying inflammation. Occasionally, it is required as initial therapy in patients with high-grade strictures, but it is often reserved for patients who failed medical therapy. Possible complications, such as deep mucosal tears and perforation, are serious limitations for wide use of this procedure.

Our clinical experience

We find it important to share our clinical practice experience with EoE and emphasize the atypical clinical presentation of the disease in the younger patients. The multidisciplinary failure to thrive (FTT) clinic at the E. Wolfson medical center includes a pediatric gastroenterologist and allergist together with a dietician, nurse, social worker and psychologist.

Among all patients referred to the FTT clinic or for gastroenterology consult between 2000 and 2010, (7,500 patients), thirty patients (23 males) aged 11 months to 20 years were diagnosed with EoE. Diagnosis was based on clinical symptoms, typical macroscopic features on esophagogastroduodenoscopy (EGD) of strictures, furrows, rings or exudates and the identification of >15 eosinophils/hpf in esophageal biopsy specimens. Data regarding this cohort, age of diagnosis, age of onset and delay in diagnosis are presented in Table 1. Diagnostic parameters, including macroscopic findings and tissue eosinophil counts, are provided in Table 2.

The high prevalence of boys in our study is similar to the data reported previously by many investigators [29, 40, 119] and may be explained by male susceptibility due to X-linked mutation in the *TSLP* receptor gene as mentioned above.

As was observed in previous studies, there was a significant delay in diagnosis in our population with a mean delay from onset of symptoms of over two years, indicating low index of suspicion for EoE diagnosis [30, 119].

The clinical symptoms varied with the age of onset infants and toddlers with symptoms onset under 3 years of age (11 patients) presented mostly (9/11) in a similar fashion with low-intake FTT. Only six had another clinical symptom that may have suggested a gastroesophageal disorder (vomiting-1, choking episodes-1, dysphagia and solid food refusal-3 and abdominal pain-1). See Table 1 for detailed data. Gastric and small bowel biopsies were normal in most of these patients (8/11).

Among children with onset between 3 and 8 years of age (7 patients), 5 had symptoms suggestive of esophageal disease such as dysphagia, heartburn, vomiting or food

Table 1 Characteristics of patients with EoE based on age of presentation

Parameter	Age groups		
	8–20 years (<i>n</i> = 12)	3–8years (<i>n</i> = 7)	1–3 years (<i>n</i> = 11)
Age diagnosis Mean $\pm$ SD years	16.3 $\pm$ 2.6	6.1 $\pm$ 1.5	1.8 $\pm$ 0.7
Age onset of symptoms Mean $\pm$ SD years	12.7 $\pm$ 4	4.5 $\pm$ 2.2	1 $\pm$ 0.6
Delay in diagnosis Mean $\pm$ SD years	3.6 $\pm$ 3.6	1.7 $\pm$ 1	0.8 $\pm$ 0.6
Gender M/F	9/3	6/1	8/3
Dysphagia or solid refusal	8	4	3
Heartburn	4	0	0
Failure to thrive	0	1	9
Poor feeding	0	0	8
Vomiting	5	2	1
Choking episodes	0	0	1
Food impaction	5	1	0
Abdominal pain	4	5	1
Food impaction	5	1	0
Abdominal pain	4	5	1
Odynophagia	1	1	0
Nocturnal cough	0	1	0

Table 2 Morphological and histological characteristics of esophageal biopsies from EoE patients

Parameter	Results
Furrows	14 (46 %)
Rings	10 (33 %)
Stricture	7 (23 %)
White exudates	17(56 %)
Distal erosions or ulcers	2 (0.67 %)
Normal morphology	6 (20 %)
Eosinophils (hpf, range)	15–140

impactions. In the children above 8 years of age (12 patients), almost all (11/12) had dysphagia, food impaction, vomiting or heartburn.

Esophageal intraluminal pH probe testing was performed in 6 children. Two of them manifested mild esophageal acid exposure, with fractional time pH < 4 of 6.8 and 9 %. The other four studies were normal. Based on clinical symptoms alone or in combination with pH monitoring 14/30 (47 %), patients had received PPI treatment prior to the referral with no clinical improvement. One continued treatment with a PPI because erosions were documented in the distal esophagus, and feeding decreased when the medication was discontinued. This patient had a

mid-esophageal stricture that improved with steroids, but dysphagia recurred after cessation.

Ten children (33 %) had a history of chronic recurrent respiratory disease including asthma and/or allergic rhinitis. Food hypersensitivity was disclosed in 17/20 (85 %) tested including milk-10, soy-3, eggs-3, chicken-3, rice-3, garlic-3, fish-2, apple-2, nuts-2, sesame-2, cocoanut-1, beef-1, banana-1, peach-1, corn-1 and olive-1.

Ten patients did not perform allergy testing (lost to follow-up or refused allergy testing). Seventeen out of thirty (56 %) responded to removal of cow's milk from their diet, regardless of the allergy tests results. Cessation of milk products led to resolution of the stricture and improvement in feeding. All but one patient received swallowed fluticasone as initial therapy (one 11 months old infants responded immediately to milk withdrawal without medical therapy). In total, three patients had received oral corticosteroids because of strictures or impactions despite inhaled steroids and dietary manipulations.

In conclusion, as it was showed previously [10], the presentation of EoE in children younger than 3 years differs from the classical presentation seen in older patients, with predominant presentation of low-intake FTT in the former group. Therefore, a high index of suspicion is needed for EoE in the young age group when evaluating a patient with unexplained low-intake FTT.

Conflict of interest None.

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