

Eosinophilic Esophagitis beyond Eosinophils – an Emerging Phenomenon Overlapping with Eosinophilic Esophagitis: Collegium Internationale Allergologicum (CIA) Update 2023

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Keywords

Eosinophilic esophagitis · Eosinophils · Eosinophilic esophagitis like · Lymphocytic esophagitis · Mast cells

Abstract

Having long been considered the mainstay in eosinophilic esophagitis (EoE) diagnosis and pathogenesis, the role of eosinophils has been questioned and might be less important than previously thought. It is well known now that EoE is a Th2-mediated disease with many more disease features than eosinophilic infiltration. With more knowledge on EoE, less pronounced phenotypes or nuances of the disease have become apparent. In fact, EoE might be only the tip of the iceberg (and the most extreme phenotype) with several variant forms, at least three, lying on a disease spectrum. Although a common (food induced) pathogenesis has yet to be confirmed, gastroenterologists and allergologists should be aware of these new phenomena in order to further characterize these patients. In the following review, we discuss the pathogenesis of EoE, particularly those mechanisms beyond eosinophilic infiltration of the esophageal mucosa, non-eosinophilic inflammatory cell populations, the new disease entity EoE-like

disease, variant forms of EoE, and the recently coined term mast cell esophagitis.

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Introduction

Eosinophilic esophagitis (EoE) is a chronic inflammatory disorder of the esophagus that is defined clinically by symptoms of esophageal dysfunction and histologically by an eosinophil-predominant infiltration of the esophageal squamous epithelium with at least 15 eosinophils per high power field (hpf) [1]. EoE is a clinico-endoscopic-histological syndrome with increasing incidence and prevalence [2, 3], occurring particularly in children and adolescents [1, 4]. The diagnosis of EoE is complex and based on a combination of typical symptoms and histological findings [5]. Patients with EoE suffer from symptoms of esophageal dysfunction, mainly solid food dysphagia up to recurrent food impactions and non-swallowing-related retrosternal pain [6]. However, EoE can also present with atypical symptoms, including abdominal pain, thoracic pain, or reflux. Such non-specific

presentation is more frequently seen in younger children; here, symptoms range from vomiting, and abdominal pain, to food refusal, and failure to thrive [7]. To diagnose EoE, an upper endoscopy has to be performed with at least 6 biopsies taken from the distal and proximal esophagus (3 biopsies each) [4]. While many patients show EoE-typical features among which are edema, furrows, exudates (inflammatory signs) and rings and strictures (fibrotic signs), upper endoscopy remains normal in a non-negligible subset of patients [8, 9]. Thus, only histology confirms the diagnosis of EoE, but a sufficient number of biopsies is key as it may present as a patchy disease. Five biopsies have been shown to result in a diagnostic accuracy of 95% [10]. Nonetheless, other conditions associated with eosinophilic infiltration of the esophagus need to be ruled out, such as (among others) gastroesophageal reflux disease (GERD), eosinophilic gastroenteritis, Crohn's disease, and systemic rheumatologic diseases [5, 6]. Current treatment options of EoE consist of the 3 Ds: drugs, diet, and dilation [11]. Swallowed topical corticosteroids and to a lesser extent proton pump inhibitors (PPI) have both been demonstrated to result in induction and maintenance of clinical and histological remission [12–15]. Most recently, an orodispersible budesonide tablet has been approved as first EoE-specific treatment in Europe [16, 17]. In the USA, the monoclonal antibody dupilumab that blocks IL-4/13 has been recently made available for the treatment of EoE [18]. Alternatively to medications, dietary restrictions can efficiently treat EoE [19, 20]. Different strategies exist, all of them limiting exposure to one or several food antigens. Finally, in patients presenting with fibrostenotic disease, (repetitive) endoscopic dilatation might remain the only treatment option [21]. However, dilations – although effective – should never be used as a single treatment modality because they do not affect underlying disease activity [22]. Having been described as a rare disease in the early 90s [23, 24], prevalence and incidence of EoE have been steadily increasing in the last 30 years [2, 3]. It is currently estimated that between one out of 2,000 and one out of 1,000 suffers from the disease [25].

While esophageal eosinophilia has long been considered the mainstay in the diagnosis and pathogenesis of EoE, the role of eosinophils has been questioned lately. Several eosinophil-targeting treatments failed to achieve clinical remission despite significant effects on eosinophilic infiltration [26–28]. Moreover, the correlation between esophageal eosinophilia and clinical disease presentation is at best moderate [29]. Finally, a novel entity clinically resembling EoE but without eosinophilic infiltration in the esophagus, so-called EoE-like disease, has been described

[30]. Thus, a particular focus in EoE research lays in the discovery of non-eosinophil-related disease mechanisms such as the role of the Th2 pathway and of non-eosinophil histological changes [31–33]. In fact, the EoE histology scoring system (EoE-HSS) has been demonstrated to better correlate with disease activity than the raw eosinophil count per hpf [34]. This is of particular interest as the EoE-HSS accounts for histological signs beyond eosinophilia including spongiosis, basal zone hyperplasia, and sub-epithelial lamina propria fibrosis. In the following review, we will discuss the pathogenesis of EoE, particularly those mechanisms beyond eosinophilic infiltration of the esophageal mucosa, non-eosinophilic inflammatory cell populations, the new disease entity EoE-like disease, variant forms of EoE, and the recently coined term mast cell esophagitis.

Pathogenesis of EoE

The pathogenesis of EoE is multifactorial and at best partially understood with numerous genetic, environmental, and immunologic components involved. The aggregation of cases of EoE within families, a disease concordance between twins [35], and the male predominance [36] suggest a considerable genetic background in EoE. Indeed, EoE disease concordance in monozygotic twins is 58%, whereas in dizygotic twins, it is estimated at 36% [35]. The risk of having a second child with EoE is 1.8–2.4% [35]. It remains unknown why the risk is higher in dizygotic twins than it is in non-twin siblings. A probable explanation could be the predominant role of concomitant environmental exposure, particularly those in early life. Several prenatal factors have been associated with an increased risk for EoE, among which are maternal fever, preterm labor, and caesarean delivery, while early life factors in the postnatal phase might also contribute to an increased risk, such as antibiotic or acid suppressant use [37]. EoE genetic susceptibility appears to be mediated through both EoE specific and non-EoE specific but general atopic disease loci, with the two having synergistic effects [38]. Genetic variants have been identified in 13 protein-coding EoE candidate risk genes, among which are CAPN14, TSLP, or LRRC32 [39, 40]. EoE genes appear to be regulated by the key EoE cytokine IL-13 [41]. In addition, CAPN14 has been shown to regulate barrier function and repair responses to IL-13 [42]. Genetic susceptibility in TSLP and CAPN14 has also been linked to the production of the proatopy cytokine IL-33, another key cytokine in early disease pathogenesis. Epithelial barrier

defects – through injury or filaggrin mutations – have been increasingly recognized as an important pathogenic mechanism in EoE [43–45]. Other factors potentially contributing to an epithelial barrier defect are changes in the esophageal microbiome, chemical compounds, changes in pH, and food additives [46, 47]. Barrier dysfunction allows antigen presentation which then results in the release of L-33 together with TSLP [48]. These cytokines lead to activation and recruitment of basophils and Th2 cells, which then secrete IL-4, IL-5, IL-13, and TGF- β [31]. T-cell population appears to be heterogenous, but two subtypes have been recently identified to be enriched in EoE based on single cell RNA sequencing: T regulatory cells and effector Th2-like cells (for details, see section on EoE beyond Eosinophils) [33]. IL-13 has long been known as the key cytokine in EoE. Among its effects are upregulation of eotaxin-3, cadherin-26, TNFAIP6, periostin, and serpin B4 [41]. Eotaxin-3 and periostin both promote eosinophil infiltration [49, 50]. Of note, IL-13-induced pathways and genes are largely reversible by swallowed topical steroid treatment [41]. IL-4 – similarly to IL-13 – is a key driver in EoE as it leads to Th2 differentiation and IgE class switching in B cells [51, 52]. Given their key role, both IL-4 and IL-13 are targeted by novel EoE medications such as the anti-IL-4 receptor alpha antibody dupilumab (blocking both IL-4 and IL-13) [53]. While IL-5 appears to have a key role in eosinophil trafficking and eosinophil survival, targeting this cytokine has only been partially effective in clinical trials [52].

Taken together, pro-inflammatory secreted products disrupt the epithelial barrier, stimulate eosinophil/mast cell infiltration, and finally promote tissue remodeling with deposition of extracellular matrix [52]. Both eosinophils and mast cells provide an additional source of TGF- β in EoE [54]. This activation of TGF- β induces increased expression of fibrotic genes and transition of fibroblasts into myofibroblasts, causing fibrosis and eventually the development of esophageal strictures [31]. IL-13 also results in downregulation of some genes, particularly filaggrin, which is important for epithelial barrier integrity, further allowing antigen penetration through the epithelium [48, 55, 56]. Epithelial barrier dysfunction is further provided by eosinophil degranulation [57]. The basal layer of the esophageal mucosa becomes hyperplastic, and its integrity as a barrier structure is impaired. This process is likely mediated by increased expression of follistatin, a natural inhibitor of bone morphogenetic protein signaling, resulting in impaired basal progenitor cell differentiation [58]. Thus, it remains an open question whether epithelial barrier defects in EoE are indeed a pathogenic mechanism or

rather a consequence of the inflammatory changes within the mucosa [43, 44, 59, 60]. Recently – however – Kaymak and colleagues reported some evidence for the role of IL-20 subfamily cytokines for the regulation of esophageal barrier function, highlighting the potential pathogenic key role of barrier dysfunction in EoE [61, 62]. Other recent advances in elucidating EoE pathogenesis include the role of Siglec-8 in eosinophil apoptosis or lysyl oxidase induction by fibroblasts resulting in fibrosis, with – however – most of the studies focusing on eosinophil infiltration or late-stage disease events [63, 64].

EoE beyond Eosinophils

Several non-eosinophilic aspects of EoE have been discovered lately. Among those are various cell types involved in EoE pathogenesis, particularly T cells. It has long been known that EoE patients exhibit higher number of T cells in the esophageal epithelium compared to healthy controls [32]. Of note, only particular subpopulations of T cells are enriched which were identified by single-cell RNA sequencing of biopsies from patients with active EoE, EoE in remission, and esophageal healthy controls [33]. Putative T regulatory cells and effector Th2-like cells were specifically increased in patients with active EoE [33]. The role of B lymphocytes is less clear than that of T cells. At least, increasing numbers of B cells have been reported with active disease [65, 66]. Upregulation of pro-angiogenic cytokines such as (among others) VEGF, FGF2, and PDGFA suggests a pro-angiogenic B-cell phenotype, which is characterized by the surface markers CD49b and CD73 [65]. Angiogenesis appears to be critical for tissue remodeling in EoE [67], although the exact role of these pro-angiogenic B cells remains to be determined. Mast cells, which are tissue-resident immune cells, are another cell type with increased density in the esophageal epithelium of EoE patients [68, 69]. Upregulation of mast cell-associated gene expression, correlation between mast cell counts and disease recurrence, and their responsiveness to EoE therapy suggest a role for mast cells in EoE pathogenesis [68]. Of note, mast cells remain activated even during disease remission [70]. They might contribute to ongoing symptoms and particularly pain, in otherwise well-controlled disease [71, 72], although this finding has been inconsistent. Expression of TRPV1 (pain-associated gene) and co-expression of CPA3 and HPGDS (as surrogate markers for mast cells) correlated in active and inactive EoE and were significantly increased in patients with pain regardless of EoE activity, while there was no such relation with eosinophilia [72]. These findings

suggest that TRPV1 and mast cells could potentially modulate pain in EoE. The role of mast cells in gastrointestinal pain has further been suggested in otherwise functional disease patients [73]. Bolton and al [71] studied children with histologically inactive EoE (defined as <15 eosinophils per hpf) and discovered that mast cell density is increased in patients with endoscopic and epithelial abnormalities, and those with persisting symptoms, despite resolution of esophageal eosinophilia after treatment. Patients with persisting endoscopic abnormalities showed significant increases in total and degranulated mast cell numbers, with no such difference seen in eosinophil counts. Mast cell count, after controlling for potential confounders, predicted the presence of furrows and rings. Total mast cell counts in patients in clinical remission were significantly lower compared to patients with either symptoms or endoscopic findings [71].

Detailed histological description and development of EoE histological scores have led to the identification of other non-eosinophilic aspects of EoE [34, 74, 75]. In fact, non-eosinophilic histological changes appear to be very specific for the disease, and consideration of these changes might result in a high correlation with disease activity [34]. These beyond-eosinophil-histological changes are spongiosis, basal zone hyperplasia, surface epithelial alterations, dyskeratotic epithelial cells, and subepithelial fibrosis of the lamina propria [34]. Taken together, a plethora of non-eosinophil mechanisms appear to play a prominent role in EoE, shifting the focus away from eosinophils as hallmark for EoE.

First Description of EoE-Like Disease

The new EoE-like phenomenon called EoE-like disease has been coined by Straumann and colleagues in 2016 [30]: 5 patients from four EoE families have been identified, presenting with EoE-typical symptoms but complete absence of eosinophilic infiltration of the esophagus. Their clinical presentation was impressive with the presence of dysphagia in all patients, even necessitating endoscopic food bolus removal in 1 patient and chest pain in 2 patients. None of these symptoms were responsive to PPI, but 4 out of 5 patients showed rapid and complete resolution upon treatment with swallowed topical corticosteroids [30]. EoE-like disease patients also lacked apparent endoscopic inflammatory or fibrotic changes normally seen with EoE. It has to be highlighted that primary motility disorders of the esophagus were ruled out in 3 patients using high-resolution manometry and pH impedance monitoring

(which were both completely normal). Interestingly, quantitative immunohistological analyses revealed a considerable infiltration with T cells, which were largely CRTH2 negative and primarily located in the peripapillary region, but only minor infiltration with mast cells [30]. Still, none of the patients qualified to be classified as having lymphocytic esophagitis. While in this case series, no signs of spongiosis or epithelial barrier defect were observed, gene expression abnormalities were comparable between classical EoE and EoE-like disease with regards to eosinophilic genes such as MUC4 and CDH26 (which are both IL-13-induced downstream cytokines) but not identical (in terms of eotaxin-3) [30]. Based on these findings, a uniform underlying pathogenesis might be assumed. The fact that 33% of the offspring of EoE-like disease patients were diagnosed with conventional EoE further suggests a possible pathogenic overlap [30].

EoE Variants

As a consequence of the aforementioned Straumann case series, a group of EoE specialists around the world collected and described their patients with EoE-like diseases [60]. For this, they used the new term EoE variants which consists of all disease entities clinically resembling EoE but not fulfilling its histological criteria. Among these variants were (1) EoE-like esophagitis (what was formerly described as EoE-like disease by the Straumann case series); (2) lymphocytic esophagitis; and (3) non-specific esophagitis. For the exact definition of these variants, see Table 1 [60]. A total of 69 patients presenting with typical symptoms for EoE (mainly dysphagia), but with absence of significant esophageal eosinophilia in esophageal biopsies, were analyzed and compared with EoE, GERD, and healthy controls [60]. Based on H&E staining, patients were classified into the three EoE variants; EoE-like esophagitis, lymphocytic esophagitis, and non-specific esophagitis. These variants were all clinically severely active. While, per definition, all adult patients suffered from dysphagia, food bolus impactions were observed in 71%. A third of patients reported chest pain. While endoscopic changes occurred in 54%, but were mainly subtle (mild rings, edema), histological changes were considerable, when assessed by the EoE-HSS score with mostly basal zone hyperplasia and spongiosis being reported [60]. Of note, subepithelial eosinophilia was assessed in 40 patients with 19 of them having detectable levels. Nonetheless, only 1 of the patients had significantly elevated eosinophilia in the lamina propria. Thus, EoE variants do not appear to be a simple

Table 1. Histological definitions of EoE variants

EoE variant	Histological definition
EoE-like esophagitis	Presence of 0–59 eos/mm ² (<15 eos/hpf), but typical histological EoE features, particularly dilated intercellular spaces and basal zone hyperplasia [30]
Lymphocytic esophagitis	Typical pattern with high number of intraepithelial lymphocytes (≥30 per hpf), gathered mainly in peripapillary fields, peripapillary spongiosis (dilated intercellular spaces) and absence of intraepithelial granulocytes [79]
Non-specific esophagitis	Histological infiltration of lymphocytes or neutrophils not fulfilling the numerical and distributional criteria of lymphocytic esophagitis [60]

subepithelial form of EoE, which might be missed by standard biopsies. In-depth analysis using immunostaining and mRNA sequencing enabled further description and characterization of these three EoE variants. In all of them, some sort of epithelial barrier dysfunction was observed. No cell infiltrates, except for T cells in lymphocytic esophagitis (per definition), were found in EoE variants (including mast cells) [60]. In addition, EPX staining ruled out the possibility of degranulated eosinophils contributing to the disease. Using next-generation mRNA sequencing, the three EoE variants were found to have distinct molecular fingerprints, partially sharing pronounced traits of EoE. Hierarchical sample clustering of RNA sequencing data finally confirmed the presence of an EoE-like (characterized by eotaxin-3 expression), non-specific, and lymphocytic variant cluster (characterized by CD3 cells and TSLP expression) [60]. Based on the considerable overlaps in the transcriptome profiles, a common underlying pathogenesis of EoE variants (and EoE) has been suggested. This ultimately raises the question of whether EoE variants and EoE are different entities or part of a disease spectrum.

Further support for this hypothesis comes from the longitudinal follow-up of EoE variant patients that was recently presented in abstract form [76]. Fifty-four patients with EoE variants had at least one available follow-up. Transition from one EoE variant (baseline) to another variant (during follow-up) occurred in more than a third of patients. In fact, in 8 patients, progression to conventional EoE was observed. While all of these patients initially presented with EoE-like esophagitis, 1 patient first developed non-specific esophagitis before progressing to conventional EoE. In addition, the frequent transition between all three EoE variants with 5 patients showing more than 1 transition suggests a diagnostic flux between the variants (and possibly EoE). Sequential mRNA sequencing analyses revealed that only a few genes are responsible for disease progression. Finally, symptomatic improvement is seen with topical

steroids in over 90% of treated patients. All of these findings further suggest the presence of a disease spectrum, where EoE only represents the most extreme phenotype.

EoE-Like Esophagitis

EoE-like esophagitis has been defined as follows: presence of 0–59 eos/mm² (<15 eos/hpf) in esophageal biopsies, but typical histological EoE features, particularly dilated intercellular spaces and basal zone hyperplasia [60]. Therefore, EoE-like esophagitis comes closest to the entity initially described by Straumann and colleagues as EoE-like disease [30]. It has been renamed in the abovementioned multicenter study to avoid the term “disease” by using the term “esophagitis” instead – in order to show its potential similarities with lymphocytic and non-specific esophagitis (see below). In contrast to the other two EoE variants, EoE-like esophagitis shows the highest risk for progression to EoE over time [76]. Thus, regular follow-up should be recommended, at least once with a repeat upper endoscopy (and esophageal biopsies). Furthermore, EoE-like esophagitis showed the highest percentage of positive subepithelial eosinophil levels [60]. Patients with EoE-like esophagitis more often had fibrosis compared to patients with other EoE variants. Cluster analyses revealed several EoE-like esophagitis-specific genes such as CXCL11, CXCL10, and CASP14. Pathogenesis of EoE-like esophagitis remains elusive, but downregulation of LEKTI – although to a lesser extent of what is seen in lymphocytic esophagitis or EoE – suggests an epithelial barrier dysfunction [60].

Lymphocytic Esophagitis

Lymphocytic esophagitis has been suggested as an EoE variant and characterized in detail in the aforementioned multicenter study [60]. For the first time, mRNA profiles

of lymphocytic esophagitis were compared with EoE, GERD, and esophageal healthy controls. Comparative analyses of mRNA sequencing datasets revealed similar upstream regulators in lymphocytic esophagitis as in the other EoE variants and conventional EoE but not GERD. Moreover, the top affected pathway in lymphocytic esophagitis (axonal guidance signaling) was also among the top five pathways changed in conventional EoE. Most upregulated genes were zinc-finger protein Gli2, the matrix metalloproteinase MMP25, and oxidative stress-associated class III β -tubulin TUBB3. In-depth analysis further revealed changes in collagens and Th2 activation, which were also found in conventional EoE [60]. In addition, epithelial barrier dysfunction was most pronounced in lymphocytic esophagitis, considerably more than in the two other EoE variants and in GERD [60].

However, despite this recent in-depth characterization, lymphocytic esophagitis has been known for several years and has usually been reported as a histologically defined entity distinct from EoE [77, 78]. The following diagnostic criteria have been proposed: presence of a lymphocyte-predominant inflammation with high number of intraepithelial lymphocytes (≥ 30 per hpf), gathered mainly in peripapillary fields, peripapillary spongiosis (dilated intercellular spaces) and absence of intraepithelial granulocytes [79]. Lymphocytic esophagitis seems to be more frequent in older women, in contrast to EoE, which is more frequent in younger men [60]. The clinical presentation is similar to EoE as dysphagia tends to be the most common symptom, but the latter is often accompanied by odynophagia [80, 81]. Although endoscopic alterations are more subtle (up to one-third of the cases present with a normal mucosa), EoE typical abnormalities such as esophageal rings, strictures, and furrows can be observed [80]. The suggested treatment modalities are similar to those used in EoE and include PPI, topical steroids, oral prednisone, and repetitive esophageal dilations [82].

Hitherto, it remains unclear whether or not lymphocytic esophagitis can clearly be classified as an EoE-related disease (variant) or if it presents a separate and distinct entity. Future studies, particularly those focusing on a long-term follow-up, will eventually help answer this open question.

Non-Specific Esophagitis

Non-specific esophagitis has been defined as follows: histological infiltration of lymphocytes or neutrophils not fulfilling the numerical and distributional criteria of

lymphocytic esophagitis [60]. Thus, this esophagitis is – as stated in its name – unspecific. However, the molecular fingerprint of this EoE variant appears to be rather specific, highlighting the presence of a distinct entity [60]. Several disease-specific genes have been identified, among which are PI15, MMP1, GALNT15. Upregulation of fibrosis pathways and particularly collagen(-related) genes suggests a strong fibrotic component. Compared to the other EoE variants, non-specific esophagitis shows lower histological disease activity when measured by the EoE-HSS (both for staging and grading) [60]. LEKTI expression is decreased, indicating an epithelial barrier dysfunction, although to a lower extent than what is seen in lymphocytic esophagitis or EoE [60]. Descriptions of disease presentation, outcome, and repetitive follow-up evaluations are urgently needed to characterize this variant in more detail, which might result in renaming it by a rather specific term.

Mast Cell Esophagitis

Mast cells are tissue-resident immune cells with increased numbers in EoE, but their exact role remains elusive [69]. More recently, a non-EoE esophagitis with marked mast cell infiltration has been observed and the entity of mast cell esophagitis has been proposed. This observation has been described in 87 patients and published in abstract form [83]. All of these patients presented with symptoms of esophageal dysfunction (mainly dysphagia and heartburn but also chest pain) but had otherwise normal endoscopy and histology. However, tryptase staining revealed a considerable mast cell infiltration in 60% of the patients (>15 mast cells per hpf) [83]. This is of particular interest given the fact that mast cells were not much increased in the case series on EoE-like disease and EoE variants. Thus, mast cell esophagitis appears to be a distinct entity. Nonetheless, in terms of age, atopic comorbidities, and female preponderance, the mast cell esophagitis patients were comparable to the patients with EoE variants [60]. As mast cells are known to be involved in allergic diseases and their role has been suggested in EoE, mast cell esophagitis might just be another phenotype within the EoE spectrum. Nevertheless, for now, this remains pure speculation and further studies, particularly studies looking at mRNA profiles, are needed to test this hypothesis. Moreover, no correlation between mast cell levels and clinical features has been found questioning their pathogenic role. At least, such correlation between cell infiltration and symptoms is far from being perfect

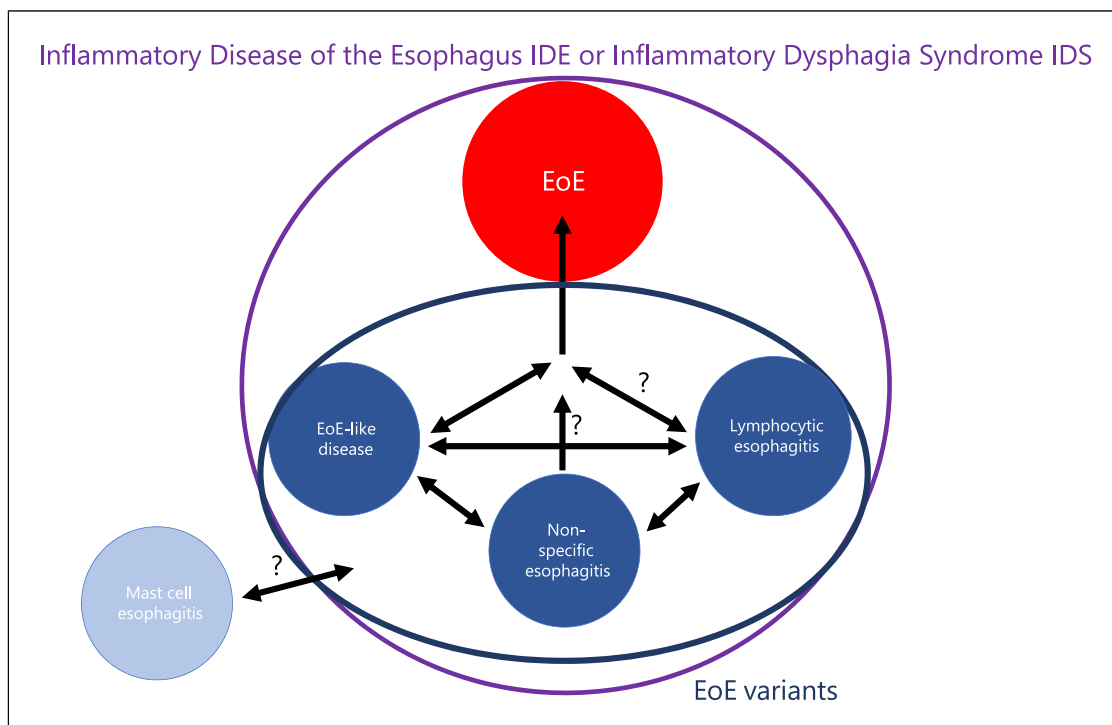


Fig. 1. Potential classification of EoE and EoE variants (EoE-like esophagitis, non-specific esophagitis, and lymphocytic esophagitis) within a larger disease spectrum (inflammatory disease of the esophagus). While transition between variants and progression from EoE-like esophagitis to EoE has been shown, it remains

unknown whether or not non-specific esophagitis and lymphocytic esophagitis can progress to EoE. In addition, the position of the recently coined term mast cell esophagitis within this classification system remains unclear.

in EoE anyway. Up to date, the position of mast cell esophagitis in relation to the other EoE variants or within the EoE spectrum remains elusive.

EoE variants and other subtypes. Given the fact that these cells can easily be missed by standard coloration, additional staining such as CD3 or tryptase immunostaining might be considered in all these patients.

Conclusions

The role of eosinophils in EoE diagnosis has been questioned and might be less important than previously thought [26–29]. Many features of a Th2-mediated disease, more than simply eosinophilic infiltration, are seen in EoE [32]. With more knowledge on EoE, less pronounced phenotypes or nuances of the disease have become apparent. In fact, EoE might be only the tip of the iceberg (and the most extreme phenotype) with several variant forms, at least three, lying on a disease spectrum (Fig. 1) [60]. Although a common (food induced) pathogenesis has yet to be confirmed, gastroenterologists and allergologists should be aware of these new phenomena in order to further characterize these patients. Re-examination of esophageal biopsies by an experienced EoE pathologist is key in order to capture the subtle non-eosinophilic features and other inflammatory cells seen in

Conflict of Interest Statement

Thomas Greuter has consulting contracts with Sanofi-Regeneron, Janssen, BMS, Takeda, AbbVie, and Falk Pharma GmbH; received travel grants from Falk Pharma GmbH and Vifor; and speaker's fee from Norgine and an unrestricted research grant from Novartis. Alex Straumann has consulting contracts with BMS, EsoCap, Falk Pharma International, and GSK. Alain Schoepfer is a consultant for Falk Pharma GmbH, Ellodi Pharmaceuticals Inc., Celgene-Receptos-BMS, and Sanofi-Regeneron. The other authors have nothing to declare. No company representative was involved in conception, writing, or financing of this study.

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Author Contributions

Vanessa Sofia Salvador Nunes: drafting the manuscript. Alex Straumann, Luis Salvador Nunes, and Alain M. Schoepfer: drafting the manuscript and critical review. Thomas Greuter: drafting the manuscript, critical review, and a responsible investigator.

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