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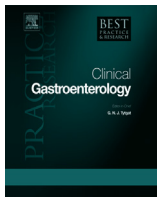

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Disease associations in eosinophilic oesophagitis and oesophageal eosinophilia

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A B S T R A C T

Eosinophilic infiltration into oesophageal tissue, typical of eosinophilic oesophagitis (EoE), has been described in several other conditions, including infections, hypersensitivity, and other autoimmune disorders. Since its description, EoE has been associated with an increasing number of diseases also characterized by tissue infiltration, including eosinophilic gastroenteritis and Crohn's disease. While an association between EoE and coeliac disease was previously reported, it is not supported by recent research. In contrast, EoE seems to be common in patients with a history of congenital oesophageal atresia, leading to hypotheses linking both disorders. The prevalence of EoE has also been shown to be eight times higher in patients with connective tissue disorders (CTDs), which has led to the proposal of an EoE-CTD phenotype, although this requires further assessment. This paper reviews the evidence of EoE's associations with several disorders, defining the common bases from an epidemiological, clinical, molecular and genetic perspective whenever possible.

Introduction

EoE has been consensually defined as a chronic, immune/antigen-mediated oesophageal disorder characterised clinically by symptoms related to oesophageal dysfunction, and histologically by an

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eosinophil-predominant inflammation [1]. In fact, oesophageal eosinophilia, that is, the presence of eosinophils in the squamous epithelium of the oesophagus, has been defined as the histological hallmark of EoE [2]. The persistence of this symptom, even after treatment with proton pump inhibitors (PPI), is required for a definitive diagnosis of EoE according to the most recent guidelines [1,2]. However, the identification and characterisation of PPI-responsive oesophageal eosinophilia (PPI-REE) represents a major breakthrough in the study of this disorder, leading to the description of a potential new phenotype within the spectrum of EoE [3].

The excessive accumulation of eosinophils in tissues is a common finding in numerous gastrointestinal disorders, including IgE-mediated food allergies, eosinophilic gastrointestinal disorders (EGIDs) [4], gastro-oesophageal reflux [5,6], and inflammatory bowel disease (IBD) [7]. In each of these processes, the pro-inflammatory functions of eosinophils may contribute to tissue damage. Because of this, a histological finding of oesophageal eosinophilia should always be interpreted within the clinical context in which it appears, since a finding of eosinophils in oesophageal biopsies alone cannot be taken as a diagnosis of EoE [8,9].

From the first descriptions of the disease, EoE has been associated with an increasing number of other diseases with different characteristics and histological features; many of these have also been associated with oesophageal eosinophilia [1,2] (Table 1). In this paper, we review evidence of EoE's association with several distinct disorders, defining the common bases from an epidemiological, clinical, molecular, and genetic perspective whenever possible.

Eosinophilic oesophagitis and coeliac disease

In recent years, several case reports and cohort studies have suggested an association between EoE and coeliac disease (CD). Whilst this association was initially reported for paediatric patients [10–14], it has since been observed in adult patients as well [13,15,16], although it has not been universally confirmed in large, population-based, epidemiological studies [17]. Even though both diseases are caused by aberrant immune responses to ingested antigens and are potentially responsive to a food elimination diet, differences in the underlying pathophysiological mechanisms leading to each of them [18,19], along with the absence of a genetic connection between EoE and CD, have prevented researchers from establishing a causal relationship [14]. In a recent systematic review assessing the relationship between EoE and CD [20], the authors found a significant publication bias in favour of studies that included small numbers of coeliac patients with an increased prevalence of EoE and vice versa. Such a bias would artificially favour the existence of an association between both disorders. Indeed, most of the studies retrieved presented a high risk of bias due to methodological backwardness, thus lacking sufficient validity to extract solid conclusions. Moreover, a recent retrospective, cross-sectional study conducted with information from a US national pathology database

Table 1
Diseases associated with oesophageal eosinophilia.

Eosinophilic oesophagitis
Gastro-oesophageal reflux disease[a]
Eosinophilic gastrointestinal diseases
Atopy
Coeliac disease
Crohn's disease
Infection
Hypereosinophilic syndrome
Achalasia
Drug hypersensitivity
Vasculitis
Pemphigoid vegetans/penphigo
Connective tissue disease
Oesophageal atresia
Graft-versus-host disease

[a] This topic will be reviewed in a different article in this issue.

demonstrated the absence of a statistically significant association between the two disorders, with an adjusted odds ratio of 1.26 (95% confidence interval: 0.98–1.60) [16].

As a result, the currently available evidence does not unequivocally support the hypothesis of an epidemiological association between EoE and CD; in fact, the study with the strongest design (a probabilistic sampling from the general population, carried out independently of patient symptoms and with a high response rate to endoscopic exploration) indicated that there was complete independence between the prevalence of the two disorders [17]. Moreover, a multicentre, observational study carried out in Spain that analysed the frequency of HLA-DQ2 and DQ8 alleles which predispose individuals to CD failed to demonstrate an increasing prevalence of such alleles in a series of 78 adult EoE patients in comparison with healthy individuals [21]. This finding rules out a common genetic basis for EoE and CD. Finally, the combined efficacy documented in the 15 studies evaluating the efficacy of a gluten-free diet in reversing EoE among coeliac patients was only 32.1% (95% confidence interval: 14.9, 52.2%) [20], which is comparable to the efficacy of restricting wheat (the second most common food trigger for EoE in both children and adults) from the diet of EoE patients [22–24].

Atopy and eosinophilic oesophagitis

From the initial descriptions of the disease, EoE has been repeatedly recognized as an atopy-associated disorder, to the point that the presence of atopic manifestations in a patient referring esophageal symptoms (especially in the form of dysphagia or food impaction) has been recognized as a characteristic marker of EoE [25]. EoE has been clearly associated with allergies in both children and adults, with peripheral eosinophilia occurring in 50% of patients [1] and elevated serum IgE levels presented in three out of four patients [1,26]. The majority of EoE patients possess a family and/or personal allergic background, commonly presenting with asthma, rhinitis, conjunctivitis and eczema with variable frequency [1]. Moreover, food and aeroallergen sensitization have been commonly described in patients of all ages [27,28]. All these data have been used to support the allergic nature of EoE, which was established after demonstrating disease remission by exclusively feeding patients with an amino acid-based elemental diet [29].

In contrast, even though food-specific IgE or skin prick test (SPT) results were positive in over 80% of adult patients [30], elimination of foods that gave positive results usually failed in achieving disease remission [31,32]. Atopic features and allergy sensitization patterns in EoE patients are not different from those atopic non-EoE individuals living in the same geographical area and exposed to common allergens [33], with no significant differences regarding history of allergic rhinitis, atopic dermatitis, immunoglobulin E-mediated food allergy or sensitization to aeroallergens, and family history of atopy found between children and adults with EoE [34]. A potential role of airborne allergens in triggering the disease has also been suggested after observing seasonal variations in the incidence of EoE [35], but these results have not been universally reproduced [36,37].

Interestingly, demographical, clinical and histopathological esophageal features are identical in EoE patients who do not associate atopic manifestations, and response to food elimination diets is equally effective in these EoE patients with negative allergy test results [24]. IgE-bearing mast cells were increased in atopic EoE patients but not in non-atopic EoE patients [38], but no differences were noted regarding mast cell counts or activation between atopic and non-atopic patients [39].

Although various atopic manifestations are present in most EoE patients, this association does not appear to have a causal relationship, but rather both diseases would present independent courses. To date, no peripheral markers have proven useful for monitoring EoE [40,41], which seems to behave like a disease restricted to the oesophagus, with few or none systemic manifestations. Common genetic and environmental etiological factors contributing to the independent development of atopy and EoE would explain the association of both entities [42,43].

Eosinophilic gastroenteritis

EoE is currently included in the broad spectrum of eosinophilic gastrointestinal disorders (EGID), a diverse group of pathologies commonly characterized by eosinophilic infiltration in different sections

of the GI tract. Symptoms of these disorders vary depending on the affected digestive segments and the involvement of different layers of the digestive wall [4,44]. In eosinophilic gastroenteritis (EGE), the affected sites are typically the stomach and small bowel, although virtually any area of the gastrointestinal tract from the oesophagus to the rectum may be involved. Because of this, the disorder occasionally presents as eosinophilic colitis [45]. First described in 1937 [46], interest in EGE has grown in recent years due to the increasing number of case reports and case series worldwide, which has partly been due to the increased recognition and diagnosis of EoE. Despite the fact that EoE is currently defined as an eosinophil-predominant inflammation restricted to the oesophagus that does not extend to distal GI segments, oesophageal involvement in a number of paediatric and adult EGE cases is well documented in the literature [47–52]. As with EoE, EGE is frequently associated with a strong family or personal history of allergy and blood eosinophilia [45]; in fact, it is sometimes considered to be a particular form of food allergy due to the predominantly proximal GI location of the eosinophilic infiltration in a significant number of patients. However, because a recent systematic review [53] found that evidence on the efficacy of dietary treatment in EGE is currently lacking, EGE cannot unequivocally be considered to be triggered and maintained by food as EoE is [32]. Thus, steroids remain the main treatment option for patients with EGE.

Currently, EoE is defined as a chronic condition in which, in the absence of treatment, the oesophageal inflammation in children progresses to fibrostenotic remodelling of the oesophagus in adulthood. Two recent retrospective studies have bolstered this hypothesis of the natural history of the disease [54,55], with persistent symptoms, endoscopic features, and oesophageal eosinophilia significantly reducing the health-related quality of life (QoL) of affected individuals over time [56–59]. In contrast, in up to 42% of EGE cases, the patients suffered a single outbreak of EGE lasting less than three months, while 37% of patients exhibited a recurrent pattern of disease, with an average of 5.2 flare-ups during extremely variable intervals. Indeed, a continuous disease course with persistent symptoms was only documented in the remaining 21% of the 43 adult study subjects with EGE who were followed for a mean period of 13 years in a recently published French study [60].

Therefore, and despite the fact that many aspects of EGE remain unknown (no definitive epidemiological figures have been established, pathophysiological data are extremely limited, and therapeutic options are mostly based on empirical experience), the evidence available to date suggest that EoE and EGE should be considered as distinct and independent disorders. From a practical point of view, every effort should be made to rule out EGE in those patients with EoE who also present symptoms in the more distal GI segments, as the therapy options and prognosis in these disorders differ substantially.

Achalasia in patients with eosinophilic oesophagitis

Various oesophageal motor disorders, including achalasia, have been sporadically reported in patients with EoE [9,61–66]. In fact, early on, researchers were already hypothesising that eosinophilic infiltration of the oesophagus was a predisposing factor for oesophageal motor disturbances [62], a proposal that has since been supported by several reports published over the last two decades. A wide range of motility abnormalities has been reported in both children and adults with EoE, most of them unspecific [67] hypercontractility and/or spastic disturbances along with reduced or absent peristalsis. Although motility disorders have been found to be more frequent in EoE patients than in controls, the prevalence and type were similar to those observed in GERD patients [68]. One exception is abnormal bolus pressurization patterns during swallowing, which seem to be more common in EoE patients and related to reduced oesophageal compliance [69].

As a specific disorder that has been defined both clinically and functionally, achalasia has been repeatedly linked with EoE. This relationship has been assessed from both sides of the issue, with EoE being identified in 3% [70] to 8% [65] of patients undergoing myotomy due to achalasia after exhibiting a poor response to conventional treatment [66]. On the other hand, achalasia has been observed in 5% [9] to 7% [71] of symptomatic patients with a dense eosinophilic infiltration in the oesophageal mucosa, among whom steroid treatment led to symptom resolution [64].

In most cases, normal oesophageal motility can be recovered with appropriate treatment for EoE.

Inflammatory bowel disease and eosinophilic oesophagitis

The presence of eosinophilic infiltration in GI tissues was recognized early on as a histopathological feature of inflammatory bowel disease [7], being described in both Crohn's disease [72] and ulcerative colitis [73,74]. In these cases, eosinophils could actually be responsible for an inaccurate prognosis [65,75]. Whilst blood eosinophil numbers may be elevated in both IBD and EoE, there is no fixed number of eosinophils that can be used as a cut-off criterion for defining disease in IBD patients, in whom the pro-inflammatory functions of eosinophils contribute to tissue damage [76].

An association between EoE and Crohn's disease has also been described in the literature [77,78], giving rise to speculation about the true relationship between the two disorders, which share an idiopathic dysregulated mucosa immune response that causes inflammation. In the first published case [78], EoE was diagnosed eight years after the patient had been suffering from Crohn's disease and was already under treatment with low doses of mesalazine. The second patient initially presented with EoE three years before being diagnosed with Crohn's disease involving the ileocolon and upper GI tract [77]. Interestingly, according to the authors, EoE improved spontaneously when the Th-1 response characterizing Crohn's disease counterregulated the Th-2 response underlying EoE.

IBD and EoE are highly prevalent disorders in Westernised countries; recent estimates indicate that IBD now affects 137–151 patients/100,000 inhabitants in Europe [79–82] and up to 241/100,000 [83,84] in the US, whilst the prevalence of EoE has been repeatedly estimated to be between 45 and 56 patients/100,000 inhabitants [27,85,86]. Curiously, the concomitance of both diseases in the same patients is so rarely described that, from an epidemiological point of view, they should be considered completely independent disorders.

The phenotype of blood eosinophils in patients with ongoing IBD (specifically ulcerative colitis), EoE, and bronchial asthma was investigated with the aid of flow cytometry in order to shed light on the pathogenic processes characterising these diseases and to define specific disease patterns of eosinophilic activation [87]. The authors found differences in the expression of surface markers that allowed them to distinguish patients with EoE and UC from one another and from healthy controls. The varying functional properties of blood eosinophils in both diseases was explained as a consequence of distinct patterns of activation signals from the inflamed tissues, providing additional evidence for the independence of the two diseases.

Infections and eosinophilic oesophagitis

GI infections and EoE seem to have an inverse association with hygienic conditions that are often dependent on socioeconomic status and allergy conditions. In this context, recent research has indicated a relationship between the development of EoE in children and reduced exposure to microorganisms during the first year of life [43]. Children with early onset EoE showed an increased activity of invariant chain natural killer T (iNKT) cells in oesophageal mucosa [88]. Because these cells act as essential regulators of mucosal responses, exposure to environmental microbial factors early in life may determine an individual's susceptibility to allergic and inflammatory diseases [89,90].

According to a recent systematic review [91], *Helicobacter pylori* (Hp) infection was associated with a significant 18% reduction in the likelihood of the development of atopy, a protective effect that was even greater for allergen specific IgE reactions. In the specific case of bronchial asthma, evidence for an inverse association with Hp infection in both children and adults was observed [92]. The protective role of Hp infection in the development of EoE has been assessed by a recent retrospective chart review of all children undergoing the first upper endoscopy procedure in a gastroenterology clinic in West Virginia (USA) [93]. The authors demonstrated a significant inverse relationship between Hp infection and EoE. A similar result was obtained in a case control study on adult Japanese patients which found a lower prevalence of Hp infection in EGE and EoE patients as compared to healthy control subjects [94]. Further studies are needed to confirm this inverse association and to investigate the mechanisms behind the protective role Hp infection seems to play against the development of EoE.

In recent years, an increasing body of evidence has indicated that untreated EoE may be a risk factor for acute infection of the oesophagus with herpes simplex virus (HSV), leading to ulcerative oesophagitis. This association has been described in paediatric patients at the time of diagnosis [95,96] and,

in contrast with common cases of HSV primary infection or reactivation, in EoE patients the infection appeared in immunocompetent individuals. This finding gives rise to the speculation that active inflammation of the oesophageal squamous epithelium may be a risk factor for acquiring HSV infections [97]. The prevention of such infections thus represents an additional reason for treating EoE.

Oesophageal atresia and eosinophilic oesophagitis

Several case reports and short case series published in the last decade have suggested that EoE is a frequent concomitant problem in patients with a history of congenital oesophageal deformities, specifically oesophageal atresia [98–102]. Oesophageal atresia, with or without an associated tracheo-oesophageal fistula, is a relatively common congenital malformation, with a live-birth prevalence of 1.8 per 10,000 births [103]. It is usually repaired soon after birth with a postoperative survival rate of 95%, which indicates that the principal burden of the disease is accounted for by post-operative morbidity. Dysphagia occurs frequently in infants and children with a history of oesophageal atresia repair; indeed, in the early postoperative period, this symptom is most commonly related to an anastomotic stricture, the development of which is related to anastomotic tension and seems to increase with gap length as well as with the presence of gastro-oesophageal reflux [104–106]. Strictures early in the life of these patients respond well to dilatations [107,108]. Later in life, dysmotility and peptic oesophagitis have been found to contribute to the development of dysphagia, so in the long term, these children are usually treated with PPI.

In the literature, most of the study subjects with both oesophageal atresia and EoE are children and adolescents, with ages ranging from 8 months to 17 years and with male patients being twice as predominant as females. A high proportion of these patients exhibit evidence of food and/aeroallergen sensitisation and peripheral eosinophilia [100–102]. Chronic dysphagia that persists after oesophageal dilation and despite having achieved a normal calibre for the oesophageal lumen was found to be common among these patients [101], who also presented endoscopic features characteristic of EoE [100]. Topical or systemic steroid treatment was effective in achieving disease resolution in most cases, although some patients concomitantly underwent food restriction guided by allergy test results or empirical six-food elimination diets.

Besides the fact that EoE should always be seriously considered when dysphagia appears later on in the life of a patient with oesophageal atresia repair and that adequate biopsies should always be taken prior to subjecting a patient to recurrent anastomotic dilatations, the association between the two conditions requires further etiological analysis.

Patients with oesophageal atresia are commonly exposed to acid gastro-oesophageal reflux, for which they usually receive maintenance therapy with high doses of PPIs [109,110]. Both factors seem to have a complex relationship with EoE [111], which should always be considered in these particular patients. Oesophageal dysmotility as a result of oesophageal atresia repair may actually prolong contact between food antigens and oesophageal mucosa, thereby predisposing these patients to EoE [112]. In addition, specific genetic similarities between oesophageal atresia and EoE have also been proposed [82]. Thus, microdeletions encompassing the Forkhead box (FOX) transcription factor gene cluster, specifically the *FOXF1* gene, have recently been shown to be associated with oesophageal atresia and other anomalies [113]. Binding sites for the gene's encoded protein, FOXF1, include not only the promoter region of genes critical for mesenchyme proliferation, but also that of genes for inflammation, including those for eotaxins and interleukin-8 [114]. Although these results were obtained from studies on mice, it is tempting to speculate about a similar role of these genes in humans; it must be remembered that eotaxin-3/CCL26 is a key chemotactic agent in attracting eosinophils towards the oesophageal mucosa in EoE and that its gene shows significant upregulation in EoE patients [115].

Connective tissue disease and Eosinophilic oesophagitis

A link between the prevalence of EoE and connective tissue disorders (CTDs), including Marfan syndrome (MFS), hypermobile Ehlers-Danlos syndrome (EDS), and joint hypermobility syndrome (JHS), has been suggested by some authors after finding an unexpectedly high (8-fold) risk of EoE in patients with CTDs (relative risk: 8.1; 95% confidence interval: 5.1–12.9) in retrospective analyses of

electronic medical record databases [116]. The study reported on a cohort of 42 patients with EoE that also suffered from a CTD-like syndrome (for which a distinct anthropomorphic phenotype was described), representing 0.8% of patients with CTDs and 1.3% of patients with EoE included in those registries. The investigation of the molecular connection of this association found mutations in fibrillin-1 (FBN1) and TGFBR1 genes, which were related to an impaired epithelial barrier function and excessive TGF-β signalling [117], respectively, with both contributing to the EoE-CTD proposed phenotype.

Further prospective research is needed to confirm the aforementioned syndromic association and to establish the particularities of EoE in these patients.

Gastrointestinal eosinophilia and graft-versus-host disease

Repeated publications have reported on the occurrence of gastrointestinal eosinophilic inflammation and peripheral eosinophilia after organ transplantation [118–121], a problem that affects all the digestive tract segments and which also involves the oesophageal mucosa. Moreover, a higher rate of graft loss in these patients has been observed; therefore, this manifestation has been explained as a local graft-versus-host disease [122]. A younger age at the time of transplantation and tacrolimus-based immunosuppression have both been related to this finding. As it is not idiopathic, but rather induced by a systemic disease or drug exposure, this phenomenon should not, strictly speaking, be considered a primary form of EGID. Whether innate immune responsiveness or an acquired immune dysregulation accounts for these findings merits further evaluation.

Practical points

- Since an excessive accumulation of eosinophils in gastrointestinal tissues constitutes a common finding in numerous disorders, a diagnosis of EoE requires that oesophageal eosinophilia be interpreted within an adequate clinical context.
- Evidence of associations between several disorders and EoE have been provided in the literature, but most of them are affected by risks of selective reporting and publication bias and need to be further assessed through well-designed prospective research.

Research agenda

- To develop wide prospective records of EoE cases is necessary for establishing the true scope and magnitude of proposed epidemiological associations between EoE and other disorders.
- The diagnostic, therapeutic, and prognostic particularities of EoE in special populations (i.e. patients with oesophageal atresia and/or connective tissue disorders) requires further research.

Conflict of interest

The author has no conflicts to declare regarding this article.

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