Eosinophilic esophagitis: current understanding and evolving concepts

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Eosinophilic esophagitis (EoE) is now considered to represent a form of food allergy and this is demonstrated by a response to elimination diet in many patients. A critical additional factor may be an inherent impairment in epithelial barrier integrity, possibly worsened by reflux of gastric contents and improved with proton pump inhibitor (PPI) use. Key clinic challenges are posed by the absence of reliable allergy tests to guide elimination diet, and the subsequent need for invasive endoscopic assessment following empirical food challenge, meaning that corticosteroids will remain the mainstay of therapy for many. From a research standpoint, determining if impairments in barrier integrity are innate, and how PPIs address this deficit (which may be pH independent) are important questions that when answered may allow future therapeutic advancement.

Key words: Food hypersensitivity; Eosinophilic esophagitis; Eosinophils; Dysphagia

INTRODUCTION

Eosinophilic Esophagitis (EoE) is a chronic inflammatory condition characterised clinically in adults by dysphagia and food bolus obstruction events and diagnosed by gastroscopy and biopsy of the esophagus [1]. Current evidence favours food antigens as the major cause of EoE, with aeroallergens and compromised esophageal barrier integrity possibly contributing to a lesser extent [2]. The recognition that proton pump inhibitors (PPIs) resolve esophageal eosinophilia in many patients, has led to the advent of a new diagnostic algorithm and disease classification approach [3]. Patients responding to PPIs are labelled as having PPI - responsive esophageal eosinophilia (PPI-REE), whilst those not responding have EoE [4]. Whether this classification distinguishes patients with an antigen driven disease from that caused by gastric acid exposure is debatable, particularly given the pleiotropic effects attributable to PPI, and early case studies suggesting that patients with PPI-REE also respond to dietary therapy usually reserved for patients with EoE [5, 6].
Gastroscopy and biopsy are mandatory both to diagnose EoE and to determine treatment response [4]. Unfortunately symptom scores are not accurate in determining disease activity [7]. Because EoE is considered to be a food antigen driven disease, allergy testing for culprit food antigens has been trialled firstly in children and most recently in adults. Unfortunately, testing for food allergy cannot be used to guide dietary therapy, but investigation for coexisting atopic conditions may be considered and symptomatic patients [8]. Seasonal rhinitis is most commonly present [9]. The first-line treatment of a patient with established EoE should arguably be with budesonide [10]. Dietary therapy, the major alternative can achieve remission in some patients but the process is cumbersome and significant expertise and infrastructure is required particularly given the need for frequent endoscopy, biopsy, and nutritional advice. If dietary therapy is considered, the 6 or 4 food elimination diet currently is advised [11]. Budesonide, best administered as a viscous slurry, by contrast will achieve histological complete remission in up 90% of patients [10]. The major disadvantage with this approach is the need for indefinite care.

The history of EoE is short, with the condition being defined in 1993, and as such significant challenges remain [12]. It would appear that the condition is becoming increasingly common irrespective of increased number of gastroscopies and physician awareness. Improvements in diagnosis, thus decreasing the need for invasive gastroscopy and discovery of allergy tests capable of detecting this condition are thus required.

DEFINITION

EoE presents in adults as dysphagia and food bolus obstruction events. The pathophysiological correlates of these symptoms are thought to comprise (1) acute narrowing of the esophageal lumen by inflammation and oedema, (2) fixed narrowing and limited distensibility of the lumen by remodelling, and (3) dynamic and variable narrowing caused by muscular contraction or spasm [13-15]. The relative contribution of these 3 pathological processes to the clinical syndrome is not known, although the focus of research and treatment relates to acute and chronic inflammation and resultant remodelling.

EoE is diagnosed only following gastroscopy and biopsy of the esophagus, where more than 15 eosinophils per high power field (HPF) are required to fulfil the diagnostic criteria, which has recently been refined to specify that an 8-week trial of PPIs be instigated prior to the biopsy to rule out the related conditions of esophageal reflux (gastroesophageal reflux) and PPI-REE [4, 16].

EPIDEMIOLOGY AND RISK FACTORS

EoE was first recognised as a distinct clinical entity only recently in 1993, and is thought to afflict between 1 in 1,000 and 1 in 10,000 children and adults, with at least 75% still affected 10 years following diagnosis [12]. Hence, the epidemiology, basic scientific and clinico-pathological data are still somewhat limited. To date, the most clearly defined risk factors for EoE are sex (male predominance), race (mainly a disease of white Caucasians), atopy (elevated serum IgE to common aeroallergens) and other allergic conditions (asthma, seasonal rhinitis, and atopic dermatitis). Other putative risk factors include: alterations in barrier function (e.g., from gastroesophageal reflux disease [GERD]); variation in the nature and timing of oral antigen exposure (e.g., secondary to infant feeding practices, PPI use and commercial food processing); variation in the nature and timing of aeroallergen exposure (seasonal, geographic and secondary to migration); alterations in microbiota (e.g., from caesarean section) and factors relating to fibrous remodelling (e.g., ACE gene polymorphisms, transforming growth factor-β polymorphisms).

What is not known is if EoE is a disease of modern life, or if the apparent increase in the last 20 years is a result of awareness by clinicians and researchers armed with modern endoscopic equipment able to make the diagnosis with the mandatory esophageal biopsy. For example, some patients who were once assumed to have GERD with stricture formation may be now called EoE. To date, several large uncontrolled retrospective studies from North America, Western Europe, and Australia demonstrate an increasing incidence and/or prevalence of EoE [17-19]. Interestingly, other atopic conditions that are better characterised such as atopic dermatitis and food allergy per se have also increased amongst children in the United States in the last 14 years [20].

EoE is a disease of both children and adults. The majority of cases diagnosed in childhood are between 5 and 10 years of age, although cases in very young children are seen [21, 22]. In adults, the mean age of diagnosis is in the late 30s, with almost all cases diagnosed before the age of 50 [8, 18]. It is notable that amongst both children and adults, EoE mainly afflicts males with a male to
female ratio of approximately 3:1 in most series [4, 23]. The distinction between adult and pediatric EoE may relate to the increased recognition of the condition, rather than 2 rigidly distinct entities. In other words, in the past, pediatric cases may have been missed and are now being diagnosed in adulthood. A recent prospective study suggests this is the case, demonstrating that EoE in more than 70% of paediatric cases remains active on transition to young adulthood over a period of 5 years’ observation [24].

The dominant theory pertaining to the likely pathogenesis of EoE is that food antigens are causative [25]. The use of an elemental diet can eliminate eosinophilic infiltration in the esophagus in up to 90% of children and 75% of adults, and the less restrictive 6 food elimination diet is successful in approximately 65% of adults and children [4]. Gonsalves et al. [8] not only demonstrated endoscopic and histological remission of the condition following successful treatment with the 6 food elimination diet, but also histological, and in many cases, observable endoscopic recurrence after reintroduction of the putative foods. The mechanism whereby food antigens are presented to the immune system and induce the characteristic eosinophil rich inflammatory cascade is a source of ongoing debate [26]. It is notable that the lower oesophagus appears to be the key focus of inflammatory activity, at least following food antigen reintroduction (after diet induced remission) [10, 27]. We speculate that this may be due to refluxate of food antigens, as the contact time of a food bolus during swallowing would be minimal. Further studies examining the relative immunopathogenic features of the upper and lower oesophagus appear warranted.

EoE can be viewed as a form of food allergy with distinct features, lacking the acute ‘allergic’ features (anaphylaxis or angioedema characteristic of classical food allergy or oral food allergy syndrome) but sharing the atopic profile of the sufferers (that is, elevation in serum IgE to aero and/or food allergens, and frequent comorbid atopic conditions such as asthma or rhinitis) [28]. As food allergy may be considered a defect of immune tolerance, and antigen exposure is a factor in the development of tolerance, the timing and magnitude of antigen exposure in shaping the immune system (e.g., the type of extent of food and aeroallergen exposure) may be important in disease pathogenesis.

It has also been proposed that aeroallergens may cause or contribute to the pathogenesis of EoE. The supportive data are limited to uncontrolled observational studies and an animal model. Case reports detail sudden symptomatic worsening following seasonal aero-allergen exposure, and sublingual immunotherapy has been hypothesised to both cause (precede the diagnosis) and cure (disappearance of EoE following the treatment of rhinitis) the condition [29-31]. Mishra et al. [32] showed that ovalbumin sensitised mice developed esophageal eosinophilia in response to airway but not gastrointestinal rechallenge. Almansa et al. [33] and Moawad et al. [34] both demonstrated a seasonal peak of EoE diagnosed at gastroscopy. The assertion of these studies is that patients with EoE present in spring/summer when aeroallergens are at their peak atmospheric concentration. Notable weaknesses of both studies are the lack of a control group and the fact that the case definition included all-comers (i.e., both newly-diagnosed and past cases). Both were also retrospective and, hence, susceptible to recall bias.

**PATHOGENESIS**

Acute as well as chronic changes appear to contribute to the characteristic clinical sequelae of dysphagia and food bolus obstruction events. Epithelial hyperplasia, inflammatory infiltrate, muscular hyperplasia and in the longer term lamina propria fibrosis appear responsible [1]. Dynamic changes including those demonstrable variably during esophageal manometry studies may be important [35].

From a theoretical standpoint, it is then apparent that the dysphagia and the food bolus obstruction events that occur in EoE may be caused by fixed narrowing (remodelling), acute narrowing (inflammation and oedema) and by esophageal dysmotility or spasm. As fixed narrowing is demonstrable at endoscopy as focal strictures, and via barium swallow as narrowing, the emphasis in research has been on remodelling. Routine esophageal manometry has not uniformly demonstrated abnormalities in patients with EoE, although Lucendo et al. [35] demonstrated high amplitude abnormal distal contractions in some patients, whilst Moawad et al. [34] demonstrated findings consistent with nutcracker esophagus in a subset of patients with a high eosinophil count [12]. Roman et al. [36] failed to demonstrate a difference in manometry findings between patients with EoE and those with GERD—both had limited peristaltic activity, perhaps demonstrating the importance of a control group. Research methodologies however, utilising
barostatic or planimetry (the assessment of esophageal distensibility) have defined abnormalities in a significant percentage of patients, with decreased distensibility and pan-esophageal pressurisation characteristic [36, 37]. Further research, particularly delineating the change in distensibility with treatment and correlation with traditional measures of treatment success (e.g., patient reports of dysphagia and eosinophil count at gastroscopy) is needed.

Acute or subacute infiltration by inflammatory cells may also explain the dysphagia and food bolus obstruction events. Significant improvement in these features has been demonstrated within 6 weeks of the commencement of dietary modification, inhaled corticosteroids and even oral corticosteroid therapy. It remains to be determined if complete symptom resolution can be achieved using these treatments, and many patients notably do not respond. The presence of eosinophils and mast cells, as well as causing inflammation and edema likely contribute to the esophageal dysfunction via the production of products of degranulation such as tryptase, major basic protein and eosinophil derived neurotoxin (see below) [38].

Correlations between the eosinophil and mast cell number and dysphagia have been noted, and future definition of this potential pathophysiological phenomenon appears important in establishing valid treatment goals [8].

**TREATMENT**

Until recently the mainstay of treatment for EoE has entailed the indefinite use of oral corticosteroids (budesonide) [39]. Failing this, esophageal dilation at endoscopy has been necessary to alleviate the dysphagia and attempt to prevent food bolus obstruction events. Two recent advances in the understanding of esophageal eosinophilia and/or EoE has meant that management guidelines have changed [4]. Firstly, high dose (twice a day) PPIs should be administered to all patients with suspected EoE, followed by gastroscopy at 8 weeks to determine if PPI-REE is present, in which case ongoing PPIs are recommended as monotherapy. Secondly, dietary therapy is now advocated as a reasonable alternative to oral corticosteroids in patients failing to respond to PPIs. In both cases however, significant knowledge deficits and practical considerations (including cost, safety, and availability of endoscopy) arguably limit the external validity of these policies (see below) [40].

PPI-REE can be demonstrated as the correct diagnosis in between 30%–90% of patients initially presenting with esophageal eosinophilia and with symptoms consistent with EoE [41]. In fact, many patients previously diagnosed with EoE and treated with corticosteroids may now arguably have their diagnosis revised should they undertake a trial of high dose PPI [10, 42]. Patients with PPI-REE are indistinguishable (according to endoscopic, histopathological and mRNA analysis) from those with disease not responding to PPIs and are thus labelled as EoE [3]. The relevance or validity of a once off endoscopy and biopsy is questionable. It is not known for example how durable this response will be. Furthermore it would be more convenient for patients if daily (thus low dose) PPIs be used, but it is not known if they will remain in remission after dose reduction. Yet another question is if these same patients would respond to dietary therapy in place of PPIs? Only high quality prospective data collection where the necessary endoscopies are performed on an adequate sample size will answer these numerous uncertainties.

Dietary therapy, usually involving the 6 food elimination diet (more rarely in severe disease amongst children, the elemental diet) has demonstrated efficacy with approximately 65% of patients achieving partial or complete remission (according to endoscopy, biopsy, and histological assessment) after 6 weeks on a modified diet [8, 43]. The use of dietary therapy, entailing the removal of specific foods, the determination of disease remission with endoscopy and biopsy, and confirmation of disease recurrence with repeat endoscopy is cumbersome and the overall uptake amongst clinicians is unknown but thought to be limited due to the obvious cost and safety concerns as well as the associated inconvenience. It has been estimated that a minimum of 8 endoscopies are required to institute the 6 food elimination diet, and the end result may be inconclusive if the response is partial (e.g., if the eosinophil count in one or more locations is between 5 and 14 eosinophils per HPF) [43]. Furthermore, the long-term acceptability of dietary therapy may be poor if multiple foods are required to be indefinitely limited (up to 1/3 of patients will have multiple food triggers) and may result in discontinuation [43]. The durability of disease remission with diet is supported by 1 adult study that demonstrated continued disease control at 12 months in 25 patients [44]. Another uncertainty is if PPIs should be continued during the trial of dietary therapy and if so when the dose should be reduced [45].

Oral corticosteroids, namely budesonide, delivered preferably as a gel at a dose of 1 mg twice daily, will result in histological
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remission in up to 90% of patients, and is well tolerated, resulting in improvement in dysphagia scores and quality of life indices [46]. Most studies have demonstrated similar levels of efficacy, and the only common side effect is oral candidiasis that can be expected in up to 30% of patients eventually, but responds readily to oral antifungal therapy [39]. Because the dose of corticosteroid is small, and as budesonide is subject to high first past hepatic elimination, the risk of hypothalamo-pituitary axis suppression appears small and has not been demonstrated in any study thus far [46]. Hence budesonide is effective treatment for EoE, albeit one that is hampered by the indefinite need for treatment. EoE will relapse upon the discontinuation of budesonide.

Esophageal dilation at endoscopy has been trialled and is an effective treatment in some patients, providing immediate relief of dysphagia [47]. Initial safety concerns, relating to the potential to cause esophageal perforation have been moderated by the publication of a retrospective cohort of 207 adult patients, with no reported perforations (significant chest discomfort and odynophagia occurred in 45% however)

CONCLUSION

EoE is a condition that has a short history and appears to be becoming increasingly common. Food as opposed to aeroallergens appear most important in causing the condition. Allergy tests have a limited role, may be more useful in guiding treatment of comorbid atopic conditions and do not reliable determine food antigen triggers of EoE. A trial of PPI followed by repeat gastroscopy in recommended in all patients to determine if PPI-REE is present. Elimination diet can induce remission in some patients but is cumbersome, requires multiple gastroscopies and arguably should be undertaken in specialist centres only. Oral viscous budesonide remains the most efficacious treatment in the routine care of patients with EoE. Given the chronic nature of the condition, significant research related resources should be directed toward better understanding EoE with a view toward diagnostic and therapeutic innovation.

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