Review paper

Food allergens and oral immunotherapy as indicators of eosinophilic oesophagitis

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Abstract

Eosinophilic esophagitis (EoE) is a chronic immune-mediated esophageal disease, clinically characterised by symptoms of esophageal dysfunction and histologically by eosinophilic infiltration of its wall. The last 3 decades have seen a sharp increase in its incidence to the point that it is called the second most common esophageal disease after reflux disease in some recent studies. The main indicators of EoE are food allergens and in recent years the extremely important role of oral immunotherapy (OIT) in the development of this disease has also been increasingly raised. To date, the appearance of EoE in the course of OIT is an absolute indication for discontinuation of this procedure; however, other therapeutic options that do not require termination of this procedure are increasingly being advocated. Unfortunately, our knowledge of EoE is full of gaps and requires numerous studies to fill in the missing elements of the pathogenesis and clinic of the described disease.

Introduction

Eosinophilic oesophagitis (EG, EoE) is a chronic immune-mediated oesophageal disease, clinically characterised by symptoms of oesophageal dysfunction and histologically by eosinophilic infiltration of its wall. The disease was first described in 1937 by Kaijser and was diagnosed as a new entity in the 1990s. It occurs more frequently in industrialised countries, more frequently in men than in women (ratio 2–3 : 1.0), and its incidence has increased rapidly in the last 3 decades (100-fold increase between 1989 and 2009) reaching a prevalence of 1 : 1000 (0.1%); as a result, in some recent studies it is called the second most common oesophageal disease after gastroesophageal reflux disease [1].

The complaints of the disease are not specific and change with age. In young children feeding difficulties, stunted growth, and weight gain predominate, while in adolescents and adults, dysphagia and episodes of food bite entrapment prevail.

According to the guidelines, the basis for the diagnosis is the histological examination of oesophageal specimens showing at least 15 eosinophils in the field of view at high magnification (400× in an area of ~0.3 mm^2). Importantly, for diagnosis, it is necessary to take at least 6 specimens from different parts of the oesophagus.

The aetiology of the disease is unknown, and the only thing we know for sure is that it coexists with allergic diseases. Commonly known evidence suggesting its association with allergy includes the following: coexisting allergic conditions, peripheral eosinophilia, elevated total IgE (tIgE), presence of specific IgE (sIgE) for inhalant allergens (more common in adults) and food allergens (more common in children), association with the pollen season, reduction of symptoms following an elimination diet, and resolution of complaints following steroid therapy. This evidence has been joined in recent years by another extremely important item, i.e. the more frequent diagnosis of EoE in patients undergoing oral immunotherapy [1].

Eosinophilic oesophagitis – aetiology

The prevalence of asthma in EoE patients is estimated to be 25–50%; food allergy is 32–37%; atopic

dermatitis (AD) is 22–27%, and allergic rhinitis (ANN) is 42–43% [2]. Patients with EoE were found to be 3 times more likely to have asthma and 5 times more likely to have ANN compared to controls. A history of food allergy in childhood has been observed to increase the likelihood of EoE frequency by as much as 9-fold, and foods that are particularly associated with the later development of EoE are milk, egg, soy, and wheat. In addition, it has been shown that children who grow out of food allergy (IgE-FA) generally develop EoE to the same allergens to which they had allergies in childhood [3]. Barbosa studied oesophageal eosinophilia in children with persistent milk allergy and found that as many as 38% had eosinophilia in biopsy specimens, and 23.5% had symptoms of EoE [4]. In Wright's study of 21 adult, asymptomatic patients with IgE-FA to peanuts undergoing screening prior to oral immunotherapy (OIT), up to 14% showed eosinophil counts > 15 in the field of view [5].

All these observations have led many researchers to call EoE "oesophageal asthma" and to include EoE in the spectrum of disorders that make up the "allergic march" as its final stage, with the average time from the diagnosis of asthma to the diagnosis of EoE estimated to be about 3 years [6].

Several theories have been put forward attempting to explain the relationship between EoE and allergic diseases, but a coherent picture is still lacking. We know that the role of food allergens in the development of EoE is indisputable and undisputed. Recently, a causal relationship between oral immunotherapy (OIT) to food allergens and the development of EoE has also been proven. A role for inhaled allergens in both the onset and exacerbation of EoE seems less certain but possible, as suggested by a study that showed an association between pollen season and the incidence of diagnosis and the timing of EoE exacerbations [7]. The development and exacerbation of EoE by inhaled allergens through a cross-reactivity mechanism with food allergens is also thought to be potentially possible [7]. Recent studies have also increasingly suggested the possibility of EoE following sublingual immunotherapy for respiratory allergies.

Eosinophilic oesophagitis – triggering foods

Many studies have tried to identify the most common foods that cause EoE. There appear to be some geographic and age differences here. It has been shown that in children in the US, EoE is most often caused by milk, eggs, and wheat, while in adults only milk and wheat [8]. The situation is different in Spain, where soy and other legumes are allergens that are more likely to be triggers of EoE [9]. Interestingly, fish, seafood, and nuts, despite being among the 6 most common allergenic foods, very rarely cause EoE. Milk is the most common allergen causing EoE (about 2/3 of patients), followed by eggs and wheat (about 25% each) and soy (about 19%) [8]. About 30–50% of patients have one food causing the disease, 30% have 2, and the remaining 25% have 3 or more foods causing EoE [8].

Eosinophilic oesophagitis – identification of the causative allergen

One of the most important problems in the diagnosis and treatment of EoE is the identification of the triggering allergen.

Identification of the causative agent on the basis of skin spot tests, sIgE, or atopic patch tests has not proven to be a good solution because the targeted diet developed on their basis has low effectiveness: in adults about 32%; in children 45%. Attempts have also been made to identify trigger foods based on identification of allergen components (for example ISAC or ALEX tests).

The ISAC and ALEX tests are molecular tests based on the determination of specific IgE antibodies in blood serum directed against single allergen components that are part of a given allergen and can induce an allergic immune response. The ISAC test includes the determination of 112 allergen components, while the ALEX test includes as many as 178 molecules and 117 allergen extracts. These are currently one of the most modern and accurate diagnostic tests in allergology, allowing the identification not of entire allergens, but of their components against which an allergic reaction develops. Although Erwin *et al.* showed more positive results for milk (mainly Bos d4 or Bos d5) compared to sIgE or spot skin tests, suggesting increased sensitivity of the test, these proteins were detected at low concentrations and were not shown to correlate with symptoms and oesophageal eosinophilia [10]. Another study showed that food elimination based on ISAC testing did not lead to a reduction in oesophageal eosinophilia [11]. The current thinking is that although the determination of allergen components shows more sensitisation, the clinical relevance and utility are still unclear [11].

Because allergy tests do not predict response to dietary treatment well, new strategies are being attempted. Two of these are showing promising results:

1. Lymphocyte proliferation test on patient serum. A positive result in either test resulted in a 53% to 75% concordance between the tests and the results of the elimination diet [12].
2. A more invasive approach was reported by the Amsterdam group: puncturing the oesophageal muco-

sa during endoscopy and administering an aqueous extract of 6 allergens directly into the oesophageal mucosa. The mucosa was observed for 20 min, and a repeat endoscopy was performed after 24 h. Immediate type reaction was observed in 5 of 8 patients, and delayed in 2 of 8 patients [13]. However, whether these reactions correlate with the results of elimination diets has not yet been established.

In view of the low usefulness of tests to identify the EoE-triggering allergen, elimination and elemental diets are still used to treat this disease.

Empirical food elimination diets (FED)

Empirical FEDs involve excluding the 6 most commonly allergenic foods (milk, eggs, soy, wheat, fish/shellfish, nuts/peanuts) from the diet. The effectiveness of such a procedure has been estimated at about 72%. The problem with this diet is the high level of dietary restriction and the high number of endoscopies after reintroduction of individual foods. In the majority (65–85%) of patients, the most common offending foods were cow's milk, wheat, eggs, and, to a lesser extent, soy/legumes; on this basis, a diet was developed excluding the 4 most common allergenic foods (4-FED: cow's milk, wheat, eggs, and legumes), and its effectiveness in adults was estimated at 54%, while in children it was 71%. On further observation, it was found that in 50% of adults and 74% of children the trigger was cow's milk, wheat, or both at the same time. Therefore, a diet with elimination of the 3 most frequently sensitised foods (3-FED) eliminating cow's milk and gluten-containing cereals was developed, resulting in remission in up to 40% of patients. It has also been shown that elimination of milk alone can also be effective in as much as 35–65% of cases [14].

If the elimination empirical diet fails, especially if rapid clinical improvement is needed, elemental diets are used. In this diet, all food allergens are eliminated by giving the allergic person amino acid mixtures. This diet is highly effective (90% lead to hist-pat remission); however, it has numerous disadvantages such as poor taste, poor quality of life associated with severe dietary restrictions, and high cost [14].

Eosinophilic oesophagitis – predictive factors

It also appears that there may be some predictors of response to elimination of the causative allergens in patients with EoE. Predictors of poorer response include a family history of food allergy and personal food allergy in a patient with positive serum sIgEs, while women and those with comorbid asthma respond better to dietary treatment [11].

Eosinophilic oesophagitis vs. oral allergy syndrome (OAS)

It was found that in the adult population with EoE, as many as a quarter (25.9%) have concurrent OAS (EoE-OAS); while in the general population, EoE occurs in 0.1% to 4.3% of adults. Patients with EoE-OAS were significantly more likely to have allergic rhinitis (but not asthma or atopic dermatitis) and higher IgE levels with the same eosinophilia count than patients with "pure" EoE. More than half (56.7%) of these individuals had reactions to more than one food. The most common triggers here were apple, carrot, peach, and banana sharing cross-reactivity with antigens from the PR-10 family of proteins, which is homologous to the major birch pollen allergen (Bet v 1). Interestingly, OAS to products that are EoE triggers is not observed [15].

Eosinophilic oesophagitis vs. inhalant allergens

There is evidence of an important role for aeroallergens in EoE, and over the past 10 years, literature has emerged describing how inhalant allergens may contribute to and exacerbate EoE in some individuals. A very high degree of comorbidity between EoE and allergic rhinitis (AR) has been demonstrated beyond the usual epidemiological relationship of (OR = 2.8). Ram *et al.* showed in a group of 1180 patients with EoE that 14% of them had a history of exacerbations caused by inhalant allergens, and 1/5 of them had biopsy-proven "seasonal" oesophageal eosinophilia [16]. Several other papers have shown a seasonal relationship of EoE with a decrease in EoE diagnosis during winter and an increase in detection during pollen seasons [17]. One study reported a significantly higher incidence of food bite tethering in people with EoE in summer and autumn compared to winter [18].

Direct evidence for the role of inhalant allergens in EoE exacerbations comes from both animal models and clinical observations, but the observations are conflicting. The development of EoE in mice has been demonstrated by exposure to year-round allergens such as cockroaches, mites, and mould [19]. In addition, the development of EoE has been observed in patients exposed to allergens such as mould, dust, and grass after sudden, accidental contact with large amounts of them [20]. In later studies, associations between inhaled allergens and the development of EoE were primarily related to pollen; no such correlation was observed with "indoor" allergens [21]. It is not entirely clear why pollen would be particularly relevant, although this may be due to cross-reactivity with components of food allergens [22]. Interestingly, a protective effect of owning a furry animal in childhood on the later development of EoE has been shown [23].

Despite this evidence, the correlation between pollen season and the frequency of EoE diagnosis is not consistent. Additionally, some studies have found no difference in the seasonal distribution of newly diagnosed EoE. Nevertheless, studies indicate that the role of inhalant allergens in EoE may be important, such as in certain groups of patients with inhalant allergy (e.g. older children and adults with allergic rhinitis), patients with seasonal inhalant allergy, and patients with inhalant or food allergies specific to certain geographic regions [24].

Eosinophilic esophagitis vs. oral immunotherapy (OIT)

Recently, there have been numerous cases of patients undergoing oral immunotherapy (OIT) who developed EoE [1]. The first studies on this problem date back to 2014. Lucendo's first meta-analysis of these studies found that EoE can develop in up to 2.7% of patients during OIT [25]. Other reviews of studies estimating cases of OIT termination due to EoE symptoms and/or positive biopsy results have shown that EoE symptoms occur at a rate of between 8% and 14% [26]. EoE is primarily triggered by OIT to food allergens (milk, egg, peanuts), with only isolated cases reporting EoE during OIT to inhalant allergens [27]. In 2018, a meta-analysis of all articles and abstracts on the development of EoE during oral immunotherapy was published. It found that symptoms suggestive of EoE occur in up to 34% of patients undergoing this procedure, and, on histopathological examination, eosinophilic infiltration characteristic of EoE occurred in up to 5.3% of patients [28].

To date, we do not know whether OIT induces EoE or inadvertently exacerbates previously asymptomatic EoE [29]. A major problem is endoscopies because they are an invasive procedure, and for proper diagnosis they should be performed before OIT and when symptoms appear, so it seems that the incidence of EoE with OIT may be underestimated. An additional problem is the side effects of OIT; due to the high number of mast cells in the gastrointestinal tract, symptoms may occur that are related to their activation rather than to the development of EoE [29]. Patients with peanut allergy have been shown to have asymptomatic eosinophilia in up to 15% already before OIT involvement [30]. Patients with food allergy are about 100 times more likely (2.6%) to develop EoE than the general population. The risk of developing EoE during OIT is estimated to be about 5% [28]. Patients who grow out of food allergy in childhood generally develop EoE to the same allergen after reintroducing the food to which they were allergic, so it happens that EoE and food allergy can co-occur in the same patient [28].

Risk factors for developing EoE during OIT appear to include the following:

- Higher levels of peripheral eosinophilia before the inclusion of treatment. An Israeli study divided patients into 4 groups according to the eosinophilia count. The correlation between eosinophilia count and gastrointestinal symptoms was as follows: Group 1: < 900 eos/mm^3 – 0.5% of patients had gastrointestinal symptoms; Group 2: 900–1500 eos/mm^3 – symptoms occurred in 15% of patients, Group 3: 1500–2500 eos/mm^3 – symptoms in 27%; and Group 4 > 2500 eos/mm^3 – symptoms in up to 46% (33% vomiting).
- Higher starting dose of allergen.
- A higher rate of allergen dose increase during the OIT and simply reducing the allergen dose by half was associated with a 90% increase in the chance of OIT success.
- Increased maintenance dose of allergen [31].

Although EoE can occur at any time in the OIT, there are clearly 2 time intervals in which EoE reveals itself more frequently:

1. Early: at the beginning of the OIT, involving most cases. It manifests with vomiting and abdominal pain. It is believed that if these symptoms occur early in the OIT and respond well to PPI treatment, then a diagnosis of EoE is unlikely.
2. Late: 2–3 years after the start of immunotherapy, involves far fewer cases. The onset of symptoms at this time makes the diagnosis of EoE more certain than for the early form [32].

The most likely mechanism in the development of EoE in the OIT appears to be dysfunction of the oesophageal epithelial barrier and secondary involvement of T lymphocytes, mast cells, and basophils. In a mouse model, repeated ingestion of food allergens further induced thymic stromal lymphopoietin, which, independent of IgE, resulted in eosinophil recruitment and infiltration and secondary fibrosis, constriction, and retention of the food bite. Unfortunately, the mechanism of EoE formation in the course of OIT is not fully known and requires further study [32].

Current guidelines recommend withholding OIT if EoE develops; however, recent work has emerged that appears to contradict this course of action. A study of 20 patients receiving peanut OIT without gastrointestinal complaints who underwent gastroscopy at weeks 0, 52, and 104 showed that at week 0, as many as 14% patients had significant but asymptomatic eosinophilia [33]. At week 52 (from the start of OIT), eosinophilia was diagnosed in 57% of the participating patients. In addition, the cited study showed that 2/3 of patients had spontaneous resolution of eosinophilia by week

104. Only one patient developed EoE requiring treatment [33]. In a study of 270 patients on peanut OIT, 37 (14%) developed symptoms suggestive of EoE, 21 (57%) discontinued the OIT, and 13 (35%) achieved resolution of symptoms after reducing the drug dose or using medications (PPIs, steroids) [34].

Thus, it seems that going forward, the final decision should be a trade-off between EoE symptoms and the risk of anaphylactic shock associated with OIT termination.

It appears that treatment options for OIT-induced EoE will include the following:

- suspension of OIT,
- continuation of OIT with modification of dosage regimen,
- continuation of OIT with a concomitant attempt to treat EoE [35].

For the continuation of the OIT, 2 options are proposed:

1. Lengthening intervals and reducing OIT doses, resulting in up to 50% complete resolution of complaints and another 15% significant relief of complaints allowing continuation of OIT [35].
2. Treatment of EoE: the first-line drug may be PPIs and, if ineffective, topical steroids [36].

Currently, the optimal approach would be to conduct screening for EoE before starting OIT. However, this is currently not possible because it would require performing gastroscopy on every patient, so other diagnostic options are being sought. The best option would be to find a marker for EoE; however, such a marker has not yet been developed. Therefore, other options are being considered, such as the following:

– string test, which involves swallowing a capsule suspended on a string and holding it in the digestive tract for several hours. After removal, an examination of the epithelium and an assessment of the number of eosinophils is made;
– cytosponge – a miniature sponge placed in the capsule, which expands after swallowing to form a sponge-like network 3 cm in diameter in the stomach. After 5 min, it is removed through the mouth with a string and the collected cells are analysed in the laboratory; determination of eosinophil precursors in peripheral blood or lymphocyte proliferation test on patients' serum is performed [37, 38].

Conclusions

EoE is one of the clinical forms of allergic gastrointestinal diseases. The last 3 decades have seen a sharp increase in its incidence. Food allergens play a major role in the development of EoE, but an increasingly important role is attributed to the OIT. In the treatment of EoE, the most important thing is to avoid the causative allergens. Diagnosis of EoE during the OIT is an indication for termination of desensitisation. However, other therapeutic options are increasingly being advocated that do not require termination of this procedure. Unfortunately, our knowledge of EoE is full of gaps and requires numerous further studies to complete.

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Conflict of interest

The authors declare no conflict of interest.

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