Review

Eosinophilic esophagitis: an update in children

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Abstract. Eosinophilic esophagitis (EoE) is an emerging antigen-mediated, inflammatory disease of unknown etiology. EoE affects about 1/2,000 patients in the United States (US), with a higher prevalence rate in adults (43.4/100,000) than in children (29.5/100,000), prevailing in Caucasians and male sex. EoE is a multifactorial disease typically characterized by type 2 inflammation. Pathogenesis is not entirely understood and is likely non-IgE mediated. Food allergens trigger EoE, stimulating the dysregulated immune cells through an impaired esophageal epithelial barrier. Clinical presentation of EoE depends on age and mainly includes food refusal, vomiting, abdominal or chest pain, dysphagia, and food impaction. Endoscopy is the gold standard to diagnose EoE. The goal of EoE therapy is to achieve clinical and histological remission to prevent esophageal fibrosis and improve patients' quality of life (QoL). Cornerstones of therapy are PPIs, topical steroids, and elimination diets. Over recent decades, research progress has been made in terms of a greater understanding of the EoE pathogenesis and new therapeutic approaches. However, there are still several unmet needs, such as non-invasive tools and biomarkers for monitoring the disease. (www.actabiomedica.it).

Keywords: Allergy, biomarkers, children, eosinophilic esophagitis, pediatrics.

Introduction

Eosinophilic esophagitis (EoE) is an emerging antigen-mediated, inflammatory disease of the esophagus characterized by chronic allergic inflammation of unknown etiology in the absence of secondary causes of esophageal eosinophilia. It is the most characterized eosinophilic gastrointestinal disorder (EGID) (1–4). EoE has become increasingly recognized in children and adults over the last decades (2,3). While in toddlers and children, EoE presents with inflammatory symptoms mimicking gastroesophageal reflux disease (GERD), in adolescents and adults, it frequently appears with food impaction, dysphagia, odynophagia, or esophageal strictures, as a consequence of the ongoing fibrosis process.

EoE is a multifactorial disorder resulting from the combination of genetic predisposition, epithelial barrier dysfunction, environmental risk factors, and allergen sensitization, leading to a type 2 (T2) inflammation of the esophagus. Histologically, EoE is characterized by dense esophageal eosinophilia with severe squamous epithelial hyperplasia (5,6). EoE is strictly associated with atopic disorders (asthma, atopic dermatitis, IgE mediated food allergy, allergic rhinitis), suggesting that EE and allergic diseases share the same environmental risk factors and early life exposures (5). Since 1993, when EoE was first recognized as a distinct clinical entity, several signs of progress in the pathophysiology of EoE were achieved; however, few studies reported data on early risk factors and how these factors might interfere with the genes in the disease onset and evolution (5).

Epidemiology of EoE

Recently, it was estimated that EoE affects about 1/2,000 patients in the United States (US), with a higher prevalence rate in adults (43.4/100,000) than in children (29.5/100,000), prevailing in Caucasians and male sex. In the last 20 years, several epidemiological studies showed a significant increase in incidence and prevalence of EoE, especially in children in Western Countries, varying widely across North America and Europe (7–9). This phenomenon might be related to an overall increased incidence of allergic and non-allergic diseases, the chronic disease course of EoE, and the improved medical awareness and knowledge through modern diagnostic instruments. Although EoE is associated with known genetic polymorphisms, this rapid increase in its frequency might indicate a prevalent role of environmental risk factors in disease development (5).

The complex pathogenesis of EoE: the role of environment and allergic inflammation

Although not entirely understood, EoE pathogenesis is multifactorial and typically characterized by a T2 inflammation (5). EoE is a non-IgE mediated disease, where food allergens trigger the esophageal inflammation and stimulate the dysregulated immune cells through the impaired esophageal epithelial barrier (5). The latter plays a crucial role in developing the disease-inducing release of thymic stromal lymphopoietin, IL-15, IL-33, which activates polarized T-helper 2 (Th2) lymphocytes and basophils with a subsequent release of inflammatory cytokines (IL-4, IL-5, IL-13) that recruits and expands eosinophilic inflammation. Therefore, this proinflammatory status leads to tissue remodeling and esophageal dysfunction (1).

A well-balanced microbiome is fundamental for the proper development of the immune system. The association between early impaired microbiota and risk of atopy is widely described for asthma, allergic rhinitis, and food allergy. Consequently, there might be a linkage between impaired microbiota and EoE, as this disease results from an atopic inflammation.

EoE epidemiology shows a higher prevalence in Western Countries, as reported for other allergic diseases. The hygienic hypothesis, postulated for the first time in 1989 by Strachan and recently reviewed, may explain the global rise of allergic and autoimmune diseases (10,11). A fewer exposition to bacterial, viral, and parasitic infections during infancy is strictly connected with the rise of allergic disease (12). An excessively hygienic environment in early life might induce adverse effects on the host microbiome, altering certain strains of necessary commensal bacteria leading to a state of dysbiosis that might be enhanced by modern lifestyle, characterized by limited physical activity, low intake of fibers, a diet high in saturated fats, and more frequent use of antibiotics (5). Primarily role of the Western diet is still debated, although foods are the primary triggers of EoE. Higher levels of fatty acids characterizing the Western diet could be related to an increased risk of developing allergic diseases. In a recent study in mice, Silva et al. demonstrated that a high-fat diet and obesity aggravated the immune histopathological characteristics and increased inflammatory cells in the EoE experimental model (13,14). Impaired microbiota might also result from early life events such as cesarean section, premature birth, early antibiotic or PPI exposure, or formula feeding. Few studies analyzed the connection between the gut microbiome and EoE. It is still not clear whether early-life risk factors might impair the esophageal microbiome, predisposing to eosinophilic inflammation and esophageal dysmotility (15-16).

Current evidence also suggested that EoE may be a complication of oral immunotherapy (OIT) in about 5% of patients or sublingual immunotherapy (SLIT) in anecdotal cases (17).

Genetic risk factors might play a pivotal role in EoE pathogenesis. EoE has a strong familiar hereditability pattern. Monozygotic twins had a 44% disease concordance and 2-fold increased risk compared to dizygotic twins. The relative risk to develop this disease in dizygotic twins may increase more than 10-fold compared to siblings (18, 19). Interestingly, EoE is also associated with several monogenic inherited diseases, especially with connective tissue disorders and skin diseases such as Marfan and Ehlers Danlos Syndrome. Also, children with autosomal dominant Hyper-IgE Syndrome (HIES) and Netherton Syndrome have

significantly increased the incidence of EoE (20, 21). Defects in PTEN, dehydrogenase E1, and transketolase domain–containing 1 (DHTKD1) gene are also associated with EoE (22)

Clinical presentation

The clinical presentation depends on age. EoE appears to be a progressive disease that persists from childhood to adulthood. This presumably reflects a difference in symptoms that result from esophageal inflammation earlier in the disease, eventually leading to fibrosis. In children and adolescents, symptoms can be protean and include food refusal, failure to thrive, nausea, vomiting, abdominal or chest pain, and heartburn (23). Dysphagia secondary to esophageal stricture becomes more prominent during the teenage years and persists into adulthood. For instance, since very young children may struggle to express complicated symptoms such as dysphagia, these symptoms may manifest themselves in food refusals for solid textures (8). EoE symptoms could be masked because the patients may have adapted compensatory feeding habits (eating slowly, excessive mastication, cutting food into small pieces) and dietary changes (preference for liquids and soft food, and avoidance of meat) to prevent the development of symptoms (24–26).

Several extraesophageal symptoms could be associated with EoE, especially respiratory symptoms. It is still unclear whether respiratory symptoms are directly caused by EoE or are coexisting allergic conditions. Indeed, the relationship between EoE and respiratory symptoms has multiple possible explanations: proinflammatory cytokines generated by the eosinophilic infiltration might trigger respiratory symptoms. Other authors point out the role of micro-aspiration, deriving in food antigens gaining direct access to the immune system via the lungs while circumventing the gastrointestinal tract (27).

EoE patients present several allergic comorbidities. Notably, 26–50% of EoE patients have concomitant asthma, 30–90% allergic rhinitis, 19–55% atopic dermatitis, and 9.8–68% IgE-mediated food allergy (28–30). Moreover, other non-atopic diseases are associated with EoE, such as inflammatory bowel disease, connective tissue disorders, autism, attention deficit hyperactivity disorder, celiac disease, and other monogenic disorders (31–35).

Recently, Biedermann et al. identified a new clinically defined syndrome in adults with EoE, called the food-induced immediate response of the esophagus (FIRE) (36). FIRE syndrome encompasses esophageal symptoms occurring rapidly after contact of the esophageal surface with a specific food. This syndrome is mainly triggered by fruits, vegetables, and drinks, just like the pollen food allergy syndrome (PFAS). Therefore, FIRE symptoms origins in the esophagus instead of the oropharyngeal cavity. Prominent symptoms are highly pronounced unpleasant and even painful retrosternal symptoms strictly linked to the ingestion of a specific food trigger, usually appearing shortly after the exposure with a latency of fewer than 5 minutes with limited duration, as most patients perceive symptoms for less than 30 minutes. Despite the limited temporal impact of symptoms, FIRE syndrome has a high intensity of pain, and patients associate other symptoms like the perception of anxiety, chest pains, or burning sensations in about 30%-40% of patients. These symptoms are also distinguished and unrelated to dysphagia and gastroesophageal reflux disease (GERD) (36,37). FIRE has been described in only one pediatric case (38). The pathogenesis of this novel syndrome is still unclear; a local immunologic factor causing an immediate mucosa response has been postulated. Moreover, FIRE may be underestimated in children because symptoms could be attributed to EoE, and patients are too young to distinguish between typical EoE, PFAS, and FIRE symptoms.

Diagnosis of EoE

The early diagnosis appears to be particularly important as EoE is a chronic disease that continues from childhood to adulthood and is characterized by a continuous esophageal remodeling. Indeed, delay in diagnosis is associated with fibrostenotic disease. The mean time from symptom onset to diagnosis of EoE was up to 3.5 years in children and eight years in adults, suggesting a need for a better understanding of the common symptoms and early indicators of the disease, which would enable clinicians to provide ear-

lier diagnosis and therefore more effective treatment as well as making patients aware of a potential underlying disease (39–41).

The gold standard for EoE diagnosis is still biopsy that demonstrates increased intraepithelial esophageal eosinophil counts without concomitant eosinophilic infiltration in the stomach and duodenum. Therefore, to formulate a proper diagnosis, excluding any secondary causes of esophageal eosinophilia is essential. Multiple esophageal mucosal biopsies (at least five or six), performed in different locations, especially in areas with mucosal abnormalities, are necessary to evaluate the peak eosinophil count, representing the current main diagnostic criterion (25). The diagnostic threshold is > 15 eosinophils/high power field (HPF). This cut-off is necessary because other condition like GERD present esophageal eosinophilia, and this threshold shows a sensitivity of 100% and specificity of 96% (42). Beyond the eosinophil count, other non-specific histologic alterations (i.e., eosinophil abscesses, basal-layer hyperplasia, dilated intercellular spaces, papillary elongation) have been associated with EoE. These abnormalities were recently scored for severity (grade) and extent (stage) in a specific scoring system (EoHSS) (24).

A wide range of endoscopic lesions is found in EoE. The most common are edema, decreased vascularity of mucosal surface, longitudinal furrows, white plaques (spots or exudate), concentric rings (trachealization), narrowing esophagus (28). In 2011, Hirano et al. proposed an endoscopic score based on a point system that notes esophageal edema, rings, exudates, linear furrows, and strictures (EREFS) that notes the presence and severity of esophageal edema has been validated extensively (43).

Therapy

EoE therapy aims to achieve clinical and histological remission to prevent esophageal fibrosis and a poor quality of life (QoL) (44–46). Therapy is likely to be lifelong; therefore, it is mandatory to achieve the best therapy with fewer side effects. Cornerstones of EoE therapy are medications (PPIs and topical corticosteroids) and diet therapy (elemental diet and food elimination diets) (1). Patients with EoE should be maintained on monotherapy when effective (47,48). However, if monotherapy fails or loses its efficacy, combination therapy may be indicated (49).

PPIs are often the first therapeutic choice, especially among patients with milder symptoms, low inflammation, and low levels of fibrosis (48,50,51). They are administrated at a high dosage (1 mg/kg/day, twice daily) and are effective in about 50% of children with EoE. Possible acid suppression side effects are dysbiosis, malabsorption, osteoporosis, and a possible higher risk for gastrointestinal and respiratory infections (52,53). Topical steroids (slurry budesonide and swallowed fluticasone) effectively induce EoE remission. They are generally well-tolerated and safe, but in long-term administration have been described few side-effects, like esophageal candidiasis that is primarily asymptomatic and discovered during the endoscopy in 1–3% of patients (54,55).

Moreover, there have been sporadic reports of decreased cortisol levels, minor anthropometric growth changes, and low bone mineral density; thus, physicians may consider periodic monitoring for growth, adrenal, and bone metabolism (54). When complete remission is achieved, topical corticosteroid treatment should be administered at the minimal effective dosage to reduce the risk of potential long-term side effects. On the other hand, a brief cycle of oral/systemic corticosteroid is also suggested for controlling refractory esophageal inflammation (1). The diet approach is effective as medication therapy (48,51). Foods are primary triggers of EoE; indeed, food elimination diets (FEDs) have demonstrated complete remission of EoE. Patients on diet therapy may potentially develop nutritional deficiencies eating disorders and experience a low QoL and high psychological impacts (7). It is mandatory to assess disease-severity, patient's nutritional status, maladaptive feeding behaviors, food allergies, family, and patient preference (2,7, 56). Children and patients should be aware of the need to undergo several endoscopic evaluations to confirm or assess disease remission (48,51).

According to current guidelines, recommended diet treatment options are elemental and empiric elimination diets (48,51).

- *Elemental diet*, which consists in removing all foods and feeding the patient exclusively with an aminoacid-based formula for at least six weeks and represents the most effective treatment with the best outcome

(90-94%) (45,49,53,54,57-59). Disadvantages are poor palatability, constipation, highly restrictive nature, costs, and psychosocial isolation, which lead to treatment discontinuation and low compliance (7,54,59).

- *An empiric elimination diet* removes the most frequent foods triggering EoE (cow's milk, egg, soy, wheat, peanuts/tree nuts, and fish/shellfish). Depending on the number of removed foods, elimination diets show an overall success rate that varies between 45 and 90%. Empiric elimination can be performed with a step-up approach, starting with eliminating the most common triggers (1 or 2 foods, such as wheat and milk) and progressively excluding other foods until histologic resolution is achieved. Otherwise, a step-down approach can be applied, starting with a highly restrictive diet (SFED) and progressing with gradual food introduction if remission is achieved (1).

The significant detriments of dietary elimination in children are nutritional deficiency, decreased quality of life, psychological impact, and the risk of feeding disorders (anorexia and bulimia, especially in adolescents) (60).

Endoscopic therapy consists primarily of esophageal dilatation in high-grade strictures or bolus release (61).

Other drug treatments have been studied, such as leukotriene receptor antagonists, biologic agents (omalizumab, infliximab, mepolizumab, reslizumab, and oral viscous sodium cromoglicate), but without showing efficacy (62–66). Although not already approved, biological therapy with dupilumab showed promising results in adults with EoE, improving symptoms, esophageal inflammation, and distensibility (67).

Conclusion

Over recent decades, research progress has been made in terms of a greater understanding of the EoE pathogenesis and new therapeutic approaches. To date, endoscopy is still the gold standard for the diagnosis and follow-up of patients with EoE. However, there are still several unmet needs, such as non-invasive tools and biomarkers for monitoring the disease. Some non-invasive biomarkers seem promising, such as galectin 10 (68). Nevertheless, none of these biomarkers has been incorporated into guideline recommendations. Moreover, multidisciplinary management of EoE is necessary, involving pediatricians, gastroenterologists, allergists, pathologists, and dietitians to optimize patient care.

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