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Review

Eosinophilic esophagitis in pediatric age, state of the art and review of the literature

Silvia Iuliano[1], Roberta Minelli[1], Francesca Vincenzi[1], Federica Gaiani[1], Claudio Ruberto[2], Gioacchino Leandro[3], Barbara Bizzarri[1], Antonio Nouvenne[1], Francesco Di Mario[1], Gian Luigi de' Angelis[1]

[1] Gastroenterology and Endoscopy Unit, Department of Medicine and Surgery, University of Parma, Parma, Italy; [2] Pediatric Emergency Unit, University Hospital of Parma, Maternal and Infant Department, Parma, Italy; [3]National Institute of Gastroenterology "S. De Bellis" Research Hospital, Castellana Grotte, Italy

Summary. Eosinophilic esophagitis (EoE) is a chronic immune-mediated relapsing disease caused by eosinophilic infiltration of the esophageal mucosa which is normally lacking these cells. EoE belongs to the group of the so called Eosinophilic Gastrointestinal Disorders (EGIDs). From a rare and unusual disease, EoE has become an emerging entity and in recent years its incidence and prevalence have increased all over the world, also in children. The pathogenesis is very complex and still not completely clear. Esophageal disfunction symptoms (e.g. dysphagia and food impaction) represent the typical manifestation of EoE and this condition could be difficult to recognize, more in pediatric age than in adults. Moreover, symptoms can often overlap with those of gastro-esophageal reflux disease (GERD), leading to a delayed diagnosis. EoE is often related to atopy and an allergological evaluation is recommended. Untreated EoE could provoke complications such as strictures, esophageal rings, narrowing of the esophagus. Diagnosis is confirmed by the demonstration in biopsy specimens obtained through upper endoscopy of eosinophilic inflammation (>15 for high powered field) of the esophageal mucosa and other histological features. Other tests could be useful not specifically for the diagnosis, but for the characterization of the subtype of EoE. Since EoE incidence and knowledge about physiopathology and natural history have increased, the goal of the review is to provide some helpful tools for the correct management in pediatric age together with an overview about epidemiology, pathogenesis, clinical, diagnosis and treatment of the disease. (www.actabiomedica.it)

Key words: eosinophilic esophagitis, food impaction, pediatric endoscopy, esophageal biopsy, eosinophils

Introduction

Eosinophilic esophagitis (EoE) is a chronic, antigen-immune inflammatory mediated disease (1) caused by infiltration of eosinophils in the esophageal mucosa (>15 eosinophils/high powered field) in absence of other causes of eosinophilia. It is characterized by esophageal dysfunction symptoms such as dysphagia, food impaction or refusal, even if gastro-esophageal reflux symptoms could be the only one referred (2). EoE is also defined as an atopic inflammatory disease and is sometimes named "asthma of the esophagus" because of shared clinical and pathophysiologic characteristics with asthma (3, 4). The first EoE cases appeared in the 1970s but it was defined as a distinct clinic-pathologic syndrome in the early 1990s. Currently, it is the most prevalent cause of esophagitis after gastro-esophageal reflux disease (GERD). Until two decades ago, it was considered a rare disorder, but its diagnosis surprisingly has increased in the last years, also in children, becoming an epidemiologically relevant disease. The exact incidence and prevalence are difficult to establish, with differences among various geographic regions. Some data show a prevalence rate of 30-90 cases per 100.000 in USA and other countries and an incidence of about 1:2000; actually,

both incidence and prevalence tend to gradually increase all over the world (2, 5). EoE seems to affect predominantly the male gender even if clear reasons of this predominance have not been understood yet; a single nucleotide polymorphism within TSLP gene (thymic stromal lymphopoietin receptor) is considered a probable etiologic mechanism, but further studies are needed. However, males are 3-4 times more commonly affected than females and caucasians are more likely affected than other races. Several studies suggest an important genetic predisposition to EoE although environmental risk factors (gut barrier function, nature and timing of oral antigen or aeroallergen exposure, impaired microbioma after physiologic events such birth) play a crucial role. In addition, the majority of patients with EoE is often affected from one or more atopic disease: asthma, eczema, allergic rhinitis and food allergies (4, 6). Children could have difficulty to report symptoms associated to esophageal dysfunction: at this age, a clinical recognition of signs is important and crucial to guide further investigations, namely and upper endoscopy, which is determinant for a certain diagnosis (7).

Pathogenesis

EoE pathogenesis is complex and not completely clear. The presence of an eosinophilic infiltration into the esophageal mucosa is crucial for diagnosis: this subtype of cells are normally absent in this gastrointestinal district (4, 8). Multiple factors as genetic, immune, environmental as well as damage mucosa and fibrosis mechanisms are involved in the onset of disease. Evidences suggest that EoE is associated with T helper cell-2 (Th2) type immune responses, which are typical of other atopic conditions. In particular, high levels of the Th2 cytokines, interleukin IL-4, IL-5, and IL-13, as well as mast cells, have been found in the esophageal biopsies of EoE patients (8, 9). These cytokines play an important role for the recruitment of eosinophils to the specific site; eosinophils are crucial cells for the remodeling of esophageal tissues. Eosinophilic granule cationic proteins, particularly the major basic protein (MBP) and the elaboration of fibrogenic growth factors are other mechanisms involved in fibrosis (8). The importance of genetic inheritance is shown by several studies: the rate of monozygotic twin concordance of inheritance of the disease is significantly increased in approximately 40% of cases and the risk of EoE is increased in people with first-degree relatives with EoE. Other single candidate genes are supposed to be involved in the pathogenesis (eotaxin-3, filaggrin, TSLP, calpain14) but their specific role remains still unclear. Indeed, several monogenic disorders with incomplete penetrance (e.g. Loeys-Dietz syndrome, Marfan syndrome, Netherton syndrome, etc) have been associated with an increased risk of EoE (4). As stated previously, there is a strong connection between EoE and atopy. Food allergens seem to be the most common triggers of mucosal inflammation in EoE and many studies have examined the benefit of dietary elimination of food allergens for the treatment of EoE (10). The link with environmental allergens is also important. Therefore, identification of EoE patient's aeroallergen sensitivities and appropriate management of allergic rhinitis can be an important step towards the prevention of flares of EoE (5, 11). EoE is substantially defined as a mixed IgE and non-IgE-mediated allergic response both to food and environmental allergens, although current literature describes that a non-IgE mediated mechanism predominate on others (12). Skin prick test (SPT) and atopy patch test (APT) to foods and/or aeroallergens result positive in many patients with EoE (4).

Clinical aspects and diagnosis

The typical onset of EoE in pediatric age occurs in childhood. Nevertheless, it could present at any age, with the type of symptoms depending on the age of presentation (13, 14). Specifically, clinical manifestations of EoE in children can vary depending on their ability to report symptoms (6). Actually, in infants and toddler or younger children, symptoms can be vague and/or ambiguous and includes feeding difficulties which could lead to prolonged mealtime, food refusal, gagging or GERD-like symptoms such as heartburn, regurgitation or vomiting (15, 16) and less commonly, failure to thrive (4). Prevalent symptoms in school aged children and adolescents include dysphagia, food

impaction, and choking/gagging with meals, particularly while eating foods with coarse texture. A careful medical history in children and adolescents with EoE reveals that they have learned to compensate for these symptoms by eating slowly, chewing excessively or taking small bites, drinking excessively with meals, lubricating meals inordinately with sauces, and avoiding specific food consistencies such as meat (or other foods with coarse texture) (17, 18). Adolescents and adults present with dysphagia (which may or not respond to medical treatment) and less frequently with food impaction. Continued dysphagia could be also caused by the formation of esophageal rings and strictures; EoE strictures could in some cases require an endoscopic dilation. However, all possible symptoms related to EoE are not relieved by anti-acid treatment with proton pump inhibitor (PPI) (5), even if sometimes patients with EoE could be asymptomatic and the diagnosis may be incidental during upper endoscopy performed for other indications, since many symptoms overlap with GERD (4). About one third of the patients with endoscopic and clinic features of EoE respond to treatment with PPI in monotherapy and this entity is referred as PPI-responsive esophageal eosinophilia (PPI-REE). It is debated if PPI-REE represents a subtype of EoE or GERD, but latest updates tend to consider it a pattern of EoE (13, 19). Recent advances in the comprehension of this heterogeneous expression of EoE lead to hypothesize a classification in phenotypes of EoE with final implications in care and response to treatment. For instance, some patients may be more prone to develop esophageal strictures whereas others do not. Additionally, some patients may respond to dietary treatment, whereas others continue to have symptoms and inflammation despite limiting specific foods. The clinical characterization of these groups may help understanding pathophysiological mechanisms and guide the therapeutic approach (20, 21). Although IgE serum level is not considered a prominent marker in EoE, a stratification risk on the basis of IgG4 serum level (an immunoglobulin that is thought to be a primary mediator of allergen tolerance but described in other non-atopic diseases) have been recently associated with active EoE. Patients with major serum levels of IgG4 have a stronger association with fibrotic clinical phenotype (22). Diagnostic evaluation for EoE requires several tools, but histological evaluation is essential. Symptoms may lead to suspect the disease, but the diagnosis is confirmed by upper endoscopy with biopsies and evidence of esophageal eosinophilia after other causes of eosinophilia and GERD have been ruled out. Other tests could be helpful depending on cases (6). Radiologic evaluation could be considered to identify focal esophageal strictures, narrowing or ring-like indentations because of its sensitivity and non-invasive approach (23-25) and to rule out the presence of a markedly narrow esophagus in severely symptomatic patients prior to endoscopy. However, barium swallow exposes to ionizing radiations and it does not allow a certain diagnosis compared to endoscopy. Several endoscopic findings are associated to EoE including esophageal edema and rings ("trachealization"), white exudate, longitudinal furrows, esophageal strictures, narrow caliber esophagus and crêpe paper esophagus. Endoscopic findings alone do not reliably establish a diagnosis of EoE. Their value to assess disease activity needs further evaluation but endoscopic reference score (EREFS) is a score system that grades the presence and severity of endoscopic features proved also in children (2, 26, 27). Biopsy specimens from both mid and distal esophagus should be obtained (26) and at least four biopsies are required to obtain adequate sensitivity for detection of EoE (also if 5-6 biopsies are still recommended) (1). The current gold standard for diagnosis of EoE is represented from an eosinophil predominant inflammation of the esophageal epithelium (cut off value of >15 eosinophils/high power field) (15). Additional histologic evaluations include basal cell hyperplasia, dilated intercellular spaces, retepeg elongation, and lamina propria fibrosis; sometimes eosinophilic microabscesses and eosinophil layering of the surface epithelium can be observed (28, 29). Allergy assessment (including patient and family medical history for atopy) is important in pediatric age, even more than in adult patients affected by EoE and is founded on Skin Prick Test (SPT) or blood testing for allergen-specific IgE, especially for patients with IgE-mediated food allergy (30). Allergy tests are discouraged if the patient does not present an history of immediate reactions. APT can be performed to study a non-IgE mediated food allergy, even if the positive predictive value remains poor (31, 32).

Treatment

Untreated EoE is usually associated with persistent symptoms and inflammation, leading to esophageal remodeling resulting in stricture formation and functional abnormalities (2) that sometimes require emergency interventions. Therapy is necessary to resolve symptoms, to induce remission and to prevent potential complications (fibrosis and esophageal strictures) (5). Strategies for treatment include: avoidance of triggered foods through dietary elimination, pharmacological therapy and mechanical dilations of the esophagus, if needed (33).

Dietary elimination

Dietary elimination (DE) can be used to induce clinical and histological remission in EoE. There are several forms of DE in EoE: elemental diet (ED), empiric dietary restrictions (EDR) and targeted dietary restrictions (TDR) based on allergy testing. ED consists in the removal of all sources of potentially allergenic protein from the patient's diet through the use of an amino acid-based formula for nutritional support (4, 5). ED achieves a high rate of clinical and histological improvement in children with EoE (>90%) but symptoms often recur after normalization of the patient's diet (31, 34). Because of the low compliance due to unpalatable taste of amino-acidic formulas, ED should be employed after considering target and empiric dietary restrictions. TDR is based on the elimination of foods resulted positive at SPT and APT and has a success rate of about 70% (although lower in adults) (35). Instead, EDR consists in the elimination of the most common allergenic foods when both SPT and APT results are negative. The first trial performed by many allergologists is cow's milk elimination, but other available strategies are the six-food elimination (dairy, eggs, wheat, soy, peanuts/tree nuts, and fish/shellfish) or four-food elimination diet (dairy, eggs, wheat, and legumes, as studies suggest tree nuts, fish, and shellfish are less commonly implicated in EoE) (36, 37, 38). EDR presents a success rate of approximately 70% (40). Open questions on DE regard the duration of the avoidance of specific foods and the correct timing for the reintroduction. Moreover, clearer indications on the management of follow-up (how often to perform endoscopy with biopsy) during the diet and the identification of potential risks of nutritional lacks are awaited.

Pharmacological treatment

Since the characterization of PPI-REE as a new entity, PPI administration is considered the first therapeutic approach for patients with EoE and it seems to induce clinical and histological remission in over 50% of cases (40, 41). In vitro, PPI seem to have an anti-inflammatory effect independently from their ability to inhibit acid production (42, 43). Treatment with corticosteroids is also an effective therapeutic option. Despite its effectiveness, systemic (oral) corticosteroids administration is associated to important side effects related to a prolonged use (44), while topical corticosteroids are confirmed to be safe and effective. Both swallowed fluticasone propionate (500-1000 μ/die) and oral viscous budesonide (1000-2000 μ/die) have been shown to be effective in EoE (19, 26). A recent meta-analysis confirmed its effectiveness in the treatment of EoE, with minimal adverse effects and no evidence of adrenal suppression (45). Patients using topical corticosteroids for EoE should be advised not to eat, drink, or rinse their mouth for 30 min after using the medication. After 6-8 weeks of topical therapy, patients should repeat endoscopy to ensure the histologic response to therapy. If a therapeutic response is confirmed, treatment should be reduced to the lowest effective dose with appropriate follow up. It is important to note that symptoms and pathological changes often recur after discontinuation of topical corticosteroids. Therefore, many patients with EoE require long-term treatment. Other tested treatments are montelukast (the leukotriene receptor antagonist) and immunosuppressive agents (azathioprine and 6-mercaptopurine) with low success rate (46, 47, 48). Biologics drugs based on use monoclonal antibodies against specific targets of the disease (IL-4, IL-5, IL-13 and IgE) have been found to be a promising option for EoE patients. While anti-IL-5 and anti-IgE monoclonal antibodies have presented controversial results in term of effec-

tiveness (49, 50, 51), others like anti-IL-13 and specifically anti-IL-4 monoclonal antibodies (dupilumab) appear the most promising novel therapeutic options for the disease, but further studied are needed to drive final conclusions (52, 53). Endoscopic dilations of EoE are required just in severely symptomatic cases or when medical treatment is not sufficient to quickly resolve symptoms (2). Dilation techniques may vary depending on age, severity of strictures and other features.

Conclusions

EoE is an emerging disease with a complex and not completely understood pathogenesis. Treatment options will continuously increase as soon as new pharmacological targets will be available. All physicians including pediatricians should be familiar with this clinical entity and manage it in cooperation with other specialists such as gastroenterologists and allergologists.

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Correspondence:
Silvia Iuliano
Gastroenterology and Endoscopy Unit,
Department of Medicine and Surgery, University of Parma
Via Gramsci 14 - 43126, Italy
Tel. +39 521 702640
E-mail: silvyul@yahoo.it