Eosinophilic esophagitis

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Abstract

Eosinophilic esophagitis is a chronic, immune-mediated disorder, isolated to the esophagus. Current theory suggests that the former may be caused by cell-mediated food hypersensitivity or may be a subset of eosinophilic gastrointestinal disease, an autoimmune disorder. During the last decade, the increasing prevalence of EoE has been recognized in pediatric populations. Reports support the efficacy of dietary restriction or corticosteroid therapy. Aditional research is needed to determine etiology, allow earlier clinical recognition and improve treatment. Because no single symptom, endoscopic finding or histopathologic feature is pathognomonic, the diagnosis can frequently be challenging. The current article reviews the possible etiology, clinical presentation, diagnosis, and treatment of this disorder, which has been called not only allergic esophagitis (which may be the most important cause), but also eosinophilic esophagitis, primary eosinophilic esophagitis, and idiopathic eosinophilic esophagitis. (Acta gastroenterol. belg., **2013**, 76, **407-412**).

Key words : epidemiology, pathogeny, clinical presentation, histologic features, diagnostic tests, thepapy.

Although eosinophils mediate the disease pathogenesis, proinflammatory cytokines are critically involved. In healthy subjects, a relatively small number of eosinophils are commonly visualized in almost all parts of the gastrointestinal tract except the esophagus. Eosinophils in the gastrointestinal tract have long been associated with intestinal inflammatory disorders, such as inflammatory bowel disease and parasitic disorders. Before 1977 esophageal eosinophilia was routinely associated with reflux esophagitis. Although the symptoms are similar to those seen in gastroesophageal reflux disease (GERD), patients experience mild or no response to acid suppression and other forms of antireflux therapy. Eosinophilic esophagitis (EoE) is a chronic, immune-mediated disorder, TH 2-type allergic inflamation, isolated to the esophagus, which is most often triggered by exposure to food antigens, present with symptoms that are similar to gastroesophageal reflux (1).

Epidemiology and pathogeny

The etiology of EoE is incompletely understand. Increasing emphasis has been placed on the role of food allergy, but EoE may also be a subset of eosinophilic gastrointestinal disease, an autoimmune disorder.

Current theory suggests that the former may be caused by cell-mediated food hypersensitivity or may be a subset of eosinophilic gastroenteritis. There are two main types of reactions : food intolerance and food hypersensitivity. More often, eosinophilic esophagitis is a form of food hypersensitivity, an immunologically mediated reaction to a food unrelated to any physiologic effect. In EoE, a type IV (cell-mediated) reaction, rather than a type I reaction (mediated by immunoglobulin E, or IgE), is most likely involved. Therefore patients with EoE have negative results on skin or radioallergosorbent (RAST) testing for IgE antibodies (2). In patients with type IV food hypersensitivity, symptoms often occur hours to days after ingestion of the causative food (mast cell activation is related) (3,4). To be clear intraepithelial mast cells counts and IgE-bearing cells may help to differentiate EoE and GERD and to define a subset of GERD patients in which an allergic component is present. Intraepithelial eosinophils and mast cells counts are significantly higher in esophageal biopsies from patients with EoE than with GERD.

During the last decade, the increasing prevalence of EoE has been recognized in pediatric populations all over the world. The prevalence is now estimated to be approaching that of Crohn disease and ulcerative colitis. Soon *et al*. in his meta-analysis have shown that the incidence of EoE in childhood varied from 0.7 to 10 per 100,000 per person-year and the prevalence ranged from 0.2 to 43 per 100,000 (5). About aged population recent data showed that EoE currently affects up to 1 in 2500 individuals in the United Stated and in Europe (6). Also, epidemiological studies demonstrated that incidence of EoE is increasing and the disease has a strong gender predilection, between 70-80% of all cases being males. One recent study showed that EoE was present in 9% of patients referred for food impaction (7).

The increasing prevalence of EoE has been correlated with the increasing prevalence of atopy. The majority of patients manifest other allergic symptoms, including asthma, rhinitis and eczema. The increasing frequency of EoE could be explained by increasing prevalence, increased awareness, or both. Provided that an increased prevalence has developed during the last decades, such a

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development may be explained by differences in food-antigen exposure, other environmental influences or genetics. Also a development within genes within a time span of a few decades seems unlikely. With regard to this disease (EoE), little is known about the environmental influence of food antigens, but a development of eating habits or food characteristics and processing may affect the propensity to develop EoE. If increased awareness is responsible, then a practical explanation could be a difference in clinical strategy, with more frequent use of upper endoscopy with biopsies. Up to one third of patients with severe EoE may have a normal-appearing of esophagus at endoscopy, thus EoE is diagnosed only if biopsies are performed.

The increasing incidence cannot be entirely explained on the new high-resolution endoscopy techniques, but the best endoscopic recognition with high resolution endoscope helps to improve the diagnosis.

Boys appear to be affected more often than girls.

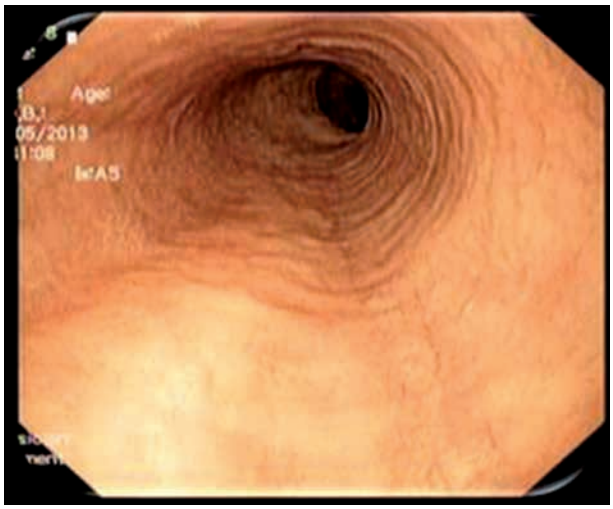

Fig. 1. — Multiple esophageal circular rings in a pacient with EoE as seen at white-light endoscopy.

Clinical presentation

Because no single symptom, endoscopic finding or histopathologic feature is pathognomonic, the diagnosis can frequently be challenging (8) In children the disease has a variety of clinical symptoms according to age : during infancy and toddler ship these are mainly feeding difficulties which can result in failure to thrive ; during childhood, vomiting and/or retrosternal pain ; during adolescence : dysphagia and food impaction.

EoE is one of the most common causes of intermittent dysphagia and food impaction in adults. Quite often the patients do not seek medical advise for their swallowing difficulties until a long lasting food impaction. It may be incorrectly diagnosed as gastroesophageal reflux disease, symptoms being present for an average duration of 4.5 years before the diagnosis is made (9).

Adults' clinical symptoms include : dysphagia, food impaction, retrosternal chest pain, refractory heartburn or upper abdominal pain, hoarseness, wheezing and hematemesis.

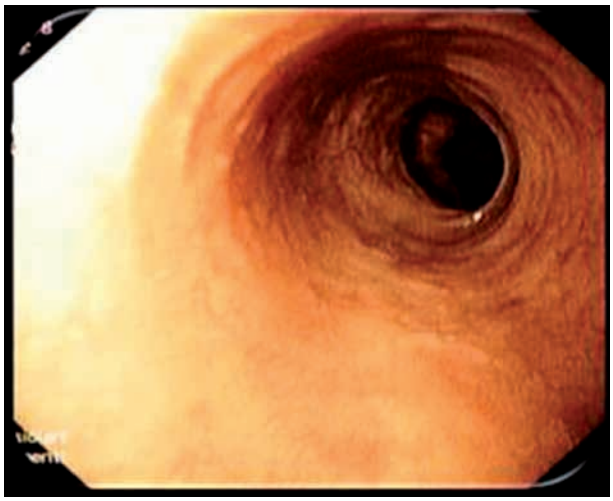

Fig. 2. — Esophageal proximal stricture in a pacient with EoE.

Histologic features

The diagnosis should be made upon symptoms, endoscopic features and histological findings. The major endoscopic aspects in EoE patients are : multiple circular rings ("feline" esophagus) – Fig. 1 and 4 ; strictures (particularly proximal strictures) – Fig. 2, whitish papules (eosinophil microabcesses) – Fig. 3, small caliber esophagus, attenuation of the subepithelial vascular pattern and linear furrows.

These features have low sensitivity for EoE, so histology remains very important in this pathology diagnosis. According to the currently recommended biopsy protocol, a total of at least 5 biopsies should be taken (10) These biopsies should be obtained from all segments of the esophagus (proximal, mid and distal) and from all endoscopically pathologic areas, such as ulcers, raised areas, or areas that may correspond to dense aggregates of eosinophils (ie, whitish papules). Also, biopsies should be obtained only after a 1-2 months of PPI treatment due to the fact that eosinophils can be present in both the EoE and GERD.

An important note is that EoE is both a clinical and pathologic diagnosis and the clinicians cannot rely exclusively on the pathologist to establish a diagnosis of EoE. A biopsy with more than 15 eosinophils per high-power field is not always diagnostic of EoE.

The histologic appearance of esophageal eosinophils has been correlated with GERD and esophagitis in children. Esophageal eosinophilia that persists despite traditional antireflux therapy may not represent treatment

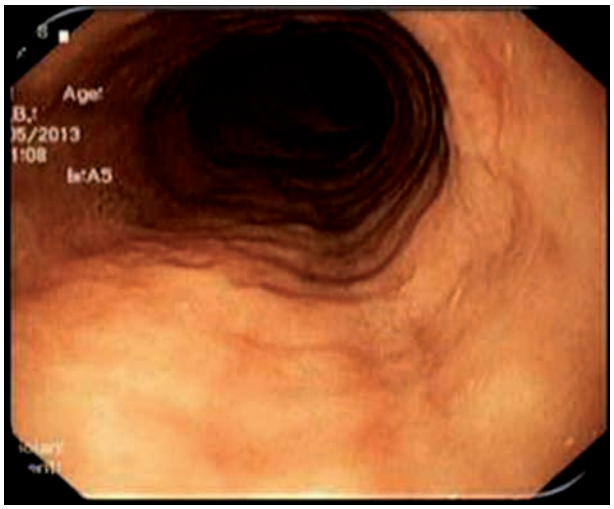

Fig. 3. — White exudates in the proximal part of the esopgahus (eosinophil microabcesses at histopathological exam).

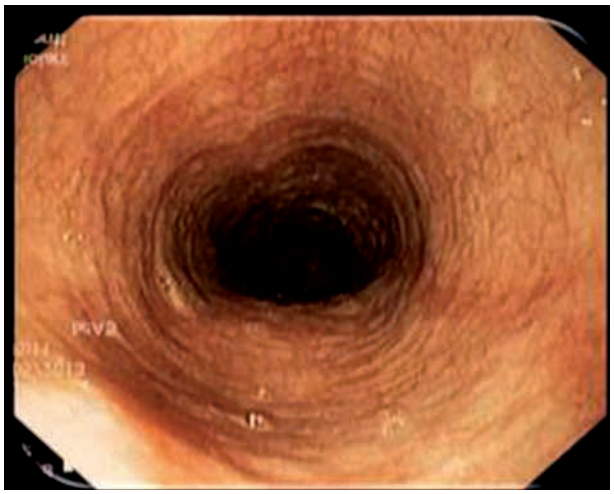

Fig. 4. — White-light endoscopy: multiple esophageal circular rings (felinization).

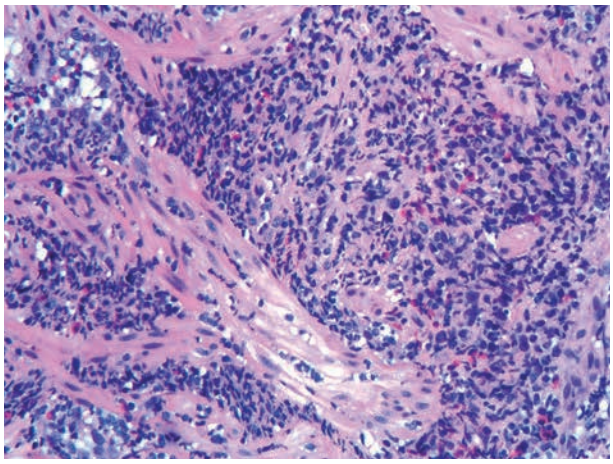

Fig. 5. — Eosinophilic microabscesses.

failure, but instead may portray early eosinophilic esophagitis or allergic esophagitis (11). For instance in children in whom gastroesophageal reflux and esophagitis are diagnosed, who do not respond to aggressive antireflux therapy, should undergo another round of testing for primary EoE. If peripheral eosinophilia develops or if important esophageal eosinophilia is noted on histologic study, EoE should be considered.

The major pathologic features of EoE include eosinophilic microabscesses, surface layering of eosinophils often associated with surface sloughing of necrotic squamous cells and peak eosinophil counts greater than 15 per high power field within the squamous epithelium (10) (Fig. 5). Minor features include marked basal cell hyperplasia, lengthening of lamina propria papillae, intercellular edema and lamina propria fibrosis with chronic inflammation (12,13).

The current diagnostic guidelines emphasize that EoE represent a clinicopathologic condition. In 2007, a multidisciplinary group of experts established the first consensus recommendations for diagnosis and treatment of EoE, which was recently updated (1).

Three criteria must be met to diagnose EoE : clinical symptoms of esophageal dysfunction, an esophageal biopsy with a maximum eosinophil count of at least 15 eosinophils per high-power microscopy field and exclusion of other possible causes of esophageal eosinophilia, including proton – pump inhibitor responsive esophageal eosinophilia (PPI-REE). A PPI trial is typically required both to evaluate for the presence of concomitant gastroesophageal reflux disease and to assess for PPI-REE (8).

EoE's less common symptoms include heartburn and chest pain. Because of this, it may be incorrectly diagnosed as a GERD. It is very important to differentiate between these two conditions because their treatments and outcomes are different. Also, the histologic features of the two diseases are very similar : although EoE often contains more eosinophils and more eosinophilic microabscesses, patients with GERD can show similar or even the same findings in certain circumstances. That is why the biopsies should be obtained only after a trial of PPI treatment for one to two months. In order to distinguish between the 2 conditions, it helps to note the distribution of the disease. GERD is typically worse in the distal esophagus and gets better as you move proximally up the esophagus ; in contrast, EoE can affect all portions of the esophagus equally, or it can even be worse proximally (compared to distally).

Diagnostic tests and therapy

EoE is most often triggered by exposure to food antigens. Exclusion of offending food antigens results in

disease remission and reexposure leads to recurrence. Because the number and nature of dietary triggers greatly vary between individuals, no "one- size-fits-all" diet has been devised that can at once eliminate the offending antigens while ensuring complete nutrition for all ages as we do on celiac disease (14). Case series have suggested an association between EoE and celiac disease in children population. Coexistent EoE should be considered in children with celiac disease who have persistent esophageal symptoms (15). Replacement of the diet by amino acid- based formula accomplishes the task, but cost, prolonged process for antigen reintroduction and the frequent need for tube feeding pose great challenges for the patient and his family (16,17).

The alternative to the elemental diet is the 6-food elimination diet (SFED). The advantage of this diet is the retention of a substantial portion of the diet, which can be nutritionally complete when managed by a dietician (18). Patient and parent education by an experienced dietician is crucial in maintaining adequate nutrition. Kagalwalla *et al*. (19) have studied the impact of this diet, which simultaneously eliminates milk, egg, soy, wheat, nuts and fish/shellfish without regard to results of traditional allergy testing. More than 75% of children experience remission of the esophageal eosinophilia while avoiding these antigens. When successful, the offending food or foods are assumed to come from these antigens. Which of the antigens is the trigger of inflammation is then determined by individual reintroduction followed by endoscopic biopsies. Another advantage of SFED is the relatively small number of endoscopies which are required to complete the process from initial withdrawal to the final restrictive diet, in contrast to the number of endoscopic biopsies needed if the entire diet was withdrawn. In conclusion, Kagalwalla' s their initial food-induced EoE. Future large-scale prospective studies addressing elimination of the 4 most common (cow's-milk protein, wheat, egg, and soy) antigens as well as studies targeting elimination of a single food (eg, cow's-milk protein) are needed to better understand and address the best dietary approach to treating this disease. There are several limitations and drawbacks associated with SFED : A very important barrier to treatment is that many children still find restricting 6 foods from the diet to be difficult and at times unacceptable, despite its temporary duration and oral route when compared with an elemental diet. Iatrogenic risks of protein energy and micronutrient deficiencies in growing children when 6 major foods, especially milk, are eliminated from the diet even temporarily remain a real concern, also. It is primarily for this reason that participation of a registered dietitian familiar with food allergies and well versed in food contamination and pediatric nutrition was essential to manage these children and prevent iatrogenic nutritional deficiencies such as kwashiorkor or rickets, which have been described in children treated for food allergies.

Philip E. Putnam (18) in his article established the frequency with which the individual antigens were responsible for eosinophilic inflammation upon reintroduction also. Milk was the most frequent and some individuals adversely reacted to 2 or more of the foods. This phenomenon is the basis for removing all 6 foods simultaneously at the outset. Antigen-avoidance diets based on allergy testing at presentation achieve a similar rate of disease remission to the SFED (20). Spergel *et al*. (21) have shown that positive predictive value of milk testing in EoE is low at 37%, therefore to attempt to optimize the SFED by current allergy testing is likely to fail. Because some individuals adversely reacted to multiple foods, withdrawal of individual foods while leaving other offenders in the diet simply perpetuates the inflammation. False-positive and false-negative allergy testing results in the failure of some elimination diets because either some offending foods remain or nonoffenders are removed unnecessarily. In either situation, repeated food trials and endoscopies are required to complete the process of establishing the final restrictive diet.

Henderson's study compared the effectiveness of 3 frequently prescribed dietary therapies (elemental, 6-food elimination, and skin prick and atopy patch-directed elimination diets) and assessed the remission predictability of skin tests and their utility in directing dietary planning.

All 3 dietary (elemental, 6-food elimination, and skin prick and atopy patch-directed elimination diets) therapies are effective ; however, an elemental diet is superior at inducing histologic remission compared with 6-food elimination and skin test-directed diets. Notably, an empiric SFED is as effective as a skin test-directed diet. The negative predictive values of foods most commonly reintroduced in single-food challenges are not sufficient to support the development of dietary advancement plans solely based on skin test results (22). To be clear I support an empiric SFED in the initial management of children who have EoE.

Because symptoms do not necessarily return in the early phase of antigen reintroduction, endoscopic biopsy, as a standard practice, has been performed to ascertain the impact of the antigen on the mucosa (18). To be clear no clinical or laboratory factor correlates well enough to replace biopsy in this disease.

A diet eliminating 6 food groups that are likely to trigger allergies may help ease the symptoms of EoE in adults also, according to a study of 67 patients with active disease. The 6 food groups (cereals, milk, eggs, fish/seafood, legumes/peanuts, and soy) were eliminated, then reintroduced sequentially, 1 at a time. Of the 67 patients, 49 (73.1%) exhibited significant drops in peak eosinophil counts before foods were reintroduced. In all, 35.71% of the patients had 1 food trigger, 30.95% had 2, and 33.3% had 3 or more. The most common food triggers, in descending order of frequency, were cow's milk, wheat, eggs, and legumes. Patients who continued to avoid the allergy-triggering foods maintained a histopathologic and clinical remission for as long as 3 years (23,24).

Biomarkers such as eotaxin-3 or eosinophil-derived neurotoxin, currently under investigation, may be useful in the future for diagnosis of EoE, without biopsy (25). In this case the restrictive diet would be identified at presentation by some form of immune response testing.

It is well established that EoE can result in lamina propria fibrosis and some patients develop fibrostenotic complications (strictures). Because the remodeling of lamina propria is reversibile with therapy, the consensus is to treat eosinophil – predominant inflammation compulsively to cause mucosa healing and prevent complications. Some patients develop fibrostenotic complications, whereas others do not. Similarly, some are clearly atopic, whereas others are not. The phenotypic variation within the population can be a possible explication (18).

Data published by von Arnim *et al*. (26) showed that a defined set of markers including two clinical features and one laboratory parameter (history of food impaction, PPI refractory symptoms and peripheral eosinophilia) is highly predictive of EoE and thus allows physicians to distinguish EoE from gastroesophageal reflux disease even before upper gastrointestinal endoscopy is performed. Unfortunately these markers may apply to adolescents and adults in whom food impaction is the main clinical symptom of EoE, but not to children of younger age.

Data published by Liacouras *et al*. (11) showed that steroid therapy may offer advantages as the initial therapy. Of 1809 patients evaluated prospectively over 2.5 years for symptoms of gastroesophageal reflux, 20 had persistent symptoms and esophageal eosinophilia, despite aggressive therapy with omeprazole. These patients were treated with 1,5 mg/kg oral methylprednisolone per day, twice daily for 4 weeks. Their results demonstrated rapid clinical and histologic improvement. By the eighth day of treatment 80% of patients reported symptom resolution. Also repeated biopsy at 4 weeks demonstrated almost complete resolution of esophageal eosinophils (from 34/HPF to 1.5/HPF). However, on discontinuation of the corticosteroid, 90% experienced a symptom relapse within 1 year.

Results with inhaled corticosteroid were reported in 4 patients with symptomatic GERD (dysphagia or pain) and important esophageal eosinophilia refractory to acid inhibition. A regimen of fluticasone, 4 puffs twice a day, produced clinical improvement, but two patients experienced relapse and required repeated inhalation therapy. Long-term follow-up data beyond 8 months were unavailable, but it is possible that chronic use of inhaled corticosteroids will be necessary.

However, systemic oral corticosteroids although very effective are not recommended in patients with EoE because of systemic side effects, and clinical and histological recurrence with discontinuation of treatment. They are reserved only for cases when immediate relief of the symptoms is required. The mainstay of steroid treatment in eosinophilic esophagitis is the off label use of topical steroids. Swallowed fluticasone propionate and oral viscous budesonide were both effective in achieving remission of eosinophilic esophagitis while, oral viscous budosenide is effective also in maintaining remission of the disease (27).

The treatment modalities of the EoE in adults include dilation, drugs and diet. Dilation can improve symptoms, but has no effect on the underlying inflammatory process. Moreover, the rate of esophageal perforation and mucosal tears during this procedure in patients with EoE is high (9). Currently, the endoscopic dilation is used only when the diet and the pharmaceutical approach have failed.

The first line medication used in present is topical steroids due to the fewer side effects (28). Unfortunately when the medication is stopped, the EoE recurrence is within a couple of months.

One study suggests that a 15-day course of treatment with budesonide is well tolerated with no serious side effects and is highly effective for remission in adolescent and adult patients with EoE (29).

Experimental evidence suggests that eosinophils play an important pathogenic role in EoE. Regulation of eosinophil maturation, recruitment and survival is under the control of interleukin-5 (IL-5). IL-5 antagonist therapies in current development, as a potential molecular target in the treatment of this disease, include two monoclonal anti–IL-5 antibodies (mepolizumab, reslizumab), a monoclonal antibody directed at the IL-5 receptor (benralizumab) and anti-sense oligonucleotide therapy (TPI ASM8) (30,31). Unfortunately, no biologic therapies currently have demonstrated significant proven benefit in EoE and thus they are not in general use (32,33).

None of the available therapies are universally effective, likely because of phenotypic variation within the population. Ongoing research should allow more precise directed initial therapy (targeting therapy to disease phenotype is crucial).

As a conclusion, dietary antigen avoidance and off – label use of topical steroids are the mainstays of therapy and seem to be durable therapies over time, although the lack of truly long-term continuous pharmacologic management studies still generates some uncertainty for its safety.

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