

POINT OF VIEW

Eosinophilic esophagitis -- clinical manifestations, diagnosis, and treatment

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ABSTRACT

Eosinophilic esophagitis (EE) is a chronic inflammatory, immunoallergic disease of the esophagus that represents the most common eosinophilic gut disease. Understanding and diagnosis regarding this condition have greatly increased in recent years, particularly in Europe and North America, in parallel with other allergic disorders. It consists of dense esophageal infiltration with eosinophils in the absence of gastro-esophageal reflux (GER). It involves individuals at all ages, and is particularly common in males during childhood and up to the 5th decade of life. It manifests with chronic, intermittent esophageal symptoms that predominantly include dysphagia, food impaction episodes, and GER-attributable complaints that do not respond to antisecretory therapy.

Endoscopically, EE is a polymorphous disease that presents with various changes in esophageal caliber, and subtle changes in mucosal appearance, which lead to biopsy collection as a key procedure for diagnosis. Management must be multidisciplinary, including gastroenterologists, pathologists, allergologists, and also nutrition specialists in pediatric cases.

Regarding therapy, dietary food restrictions are especially useful in the management of pediatric EE, but effectiveness is lower in the adult, maybe because of a greater involvement of air allergens. Drug use is standard, particularly involving topical steroids, which may revert manifestations and histological lesions, even though recurrence following discontinuation is common.

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INTRODUCTION

The esophagus is a muscular organ that channels food from the pharynx to the stomach as a result of its anatomical structure, which is particularly adapted to motor function. Its squamous, stratified epithelial lining resembles the skin, lacks absorptive structures, and has scarce submucosal acinar glands that secrete lubricating mucus and bicarbonate. The contraction of its muscle layers, coordinated by Meissner's and Auerbach's plexuses, results in movements that advance the swallowed bolus by sequentially activating esophageal segments.

The gut wall is an extensive contact area with the outer environment whose primary role is serving as a physical barrier, and which also possesses mechanisms to identify the various substances and organisms contacted, to which it may respond for or against. The gut mucosa has a number of specialized structures and functions regarding this role, and permanently lodges cells of various immune stocks that warrant these functions. However, the esophageal wall's content in such cells is virtually negligible when compared to distal gut segments characterized by absorptive functions. While little attention has been traditionally paid to the role of the esophagus in immune responses, this organ also has a surveillance system, and inflammatory infiltration by eosinophils reflects an induction of its immune capacity.

We may define eosinophilic esophagitis (EE) as a chronic esophageal inflammatory disorder, immunoallergic in nature and of unknown origin that is characterized by dense infiltration by eosinophilic granulocytes that is restricted to the esophagus. This inflammation develops in the absence of pathological gastro-esophageal reflux (GER), and the condition presents with various esophageal and upper gastrointestinal tract complaints of highly variable frequency and duration (1).

EOSINOPHILIC ESOPHAGITIS: HISTORICAL NOTES

Esophageal eosinophilic infiltration has a recent history. Its first mention in the literature was in 1977 when a 51-year-old male was described who had dysphagia and chest pain, a history of asthma and environmental allergy (2), and eosinophilic gastroenteritis (EG) with esophageal involvement. During the 1980s a number of papers defined the presence of eosinophils permeating the esophageal epithelium as a pathognomonic sign of gastro-esophageal reflux (3). This consideration represented a complication for the correct identification of many patients with esophageal eosinophilic infiltration who did not respond to conventional antisecretory therapy (4,5). It was the work by Attwood et al. (6) that first defined EE as a distinct clinico-pathological syndrome that was independent from EG when they described 12 young patients with severe eosinophilic infiltration exclusively restricted to the esophagus, to a significantly greater extent than in GERD, and with distinct clinical characteristics. It was only one year later that Straumann et al. (7) published a paper on 10 patients with recurrent acute dysphagia; already in 1994, they noted that the prevalence of EE was underestimated, as this could be considered the most common form of eosinophilic enteropathy, and predicted greater recognition in the future. Shortly afterwards, Kelly et al. (8) described 10 children with esophageal eosinophilia and severe, long-standing GER symptoms refractory to anti-GER drugs and Nissen fundoplication, who after being fed with amino-acid mixtures lacking antigenic power for at least 6 months showed resolved ($n = 8$) or improved ($n = 2$) symptoms, epithelial eosinophilic infiltration, and mucosal reactive changes. Symptoms developed again on returning to a normal diet, which defined esophagitis from severe reflux with eosinophilia as a form of food allergy. The number of cases reported in the literature has continued to grow exponentially ever since.

EE has been considered an emergent disease (9,10). However, its increased epidemiology also results from a better understanding of this disease by clinicians, who now consider it within the differential diagnosis of dysphagia, and of course by pathologists, a key part in the diagnostic process (11). During the last few years, figures available on the prevalence and incidence of this condition in developed countries have progressively increased: In 2004, Straumann et al. (12) estimated a prevalence of 1.43 cases/ 10^4 inhabitants/year among the Swiss adult population, similar to that seen in our healthcare area in Madrid (1.8 cases/ 10^4 inhabitants/year) (13) a year later. In the pediatric population the incidence in the USA for 2005 was estimated as 10 cases/ 10^4 inhabitants/year, with a cumulative prevalence of 43 patients/ 10^5 . Reports during the last year estimate prevalence above 90 cases/ 10^5 inhabitants (14). However, we should here highlight the results from a recent epidemiological study performed in

Sweden, which estimates that up to 1 in every 100 inhabitants at Kalixandra had histological findings consistent with eosinophilic esophagitis in their biopsies regardless of symptoms (15).

EE cases reported in the literature are mainly from countries in Europe and North America, and to a lesser extent in Asia, South America, and Australia. This distribution affecting most developed areas parallels bronchial asthma and other atopic conditions, hence we may involve environmental and immune factors in common with other allergy forms in its etiopathogenesis (16).

More than 65% of EE cases develop during childhood (17), but the condition has also been described in patients of all ages (18). In contrast to other immunoallergic diseases, EE predominates in males regardless of age (more than $\frac{3}{4}$ of cases), and most commonly presents in adults during the 3rd to 5th decades of life (19).

ETIOLOGY

Multiple evidence supports the consideration of EE as an allergic disorder: a great majority of patients, both adults and children, have a personal and/or family history of atopy (asthma, rhinitis, conjunctivitis, drug and food allergies) (20,21), frequent food (22,23) and/or air allergen sensitization (24), blood eosinophilia, increased serum IgE levels, and positive results in multiple allergy skin tests and RAST. Elemental dieting, absence of selected foods, and anti-allergy therapies result in clinical and histological remission (25). In addition, parallel esophageal and bronchial eosinophilic inflammation has been reported for some EE patients on a seasonal basis (26,27), as well as its development after food (28) or drug (29) ingestion. On all these grounds EE has been considered an immunoallergic disorder.

CLINICAL MANIFESTATIONS

EE is characterized by a number of nonspecific esophageal symptoms, both acute and chronic, that develop at highly variable ages (30). Also, these symptoms have a number of differences according to patient age. An extensive review of EE reported in 2002 (31) found that symptoms in adults included dysphagia, food impaction, vomiting, and chest pain, whereas children also have nausea, heartburn, epigastric pain, sialorrhea, food aversion, delayed growth, and respiratory complaints (cough, stridor, sinusitis, obstruction, pneumonia). Patients commonly have a number of simultaneous EE-related symptoms at any age.

In children, the ability to effectively report symptoms determines various presentation forms for pediatric EE (32), hence the possibility of a time sequence for EE

manifestations has been proposed (33); thus, smaller children (who cannot report dysphagia) would have a number of eating disorders including food aversion; later on, vomiting, regurgitation, and both chest and abdominal pain, mimicking gastro-esophageal reflux disease (GERD); from 11 years on, the condition would manifest with dysphagia and food impaction, which predominate in adults. It should be noted that patients eat dead slow, taking much longer than the rest of the family to complete a meal, and usually drink after each and every bite; parents should be asked for this during history-taking.

In adult patients intermittent dysphagia is the most common complaint, and occurs in more than 70% of cases in some series; however, food impaction is the symptom that most often leads to a diagnosis (56 to 88% of cases) (34). While less frequent, GERD symptoms are also commonplace (35). Overall, symptoms persist for a long time, even years, before a diagnosis is reached (36). Much less common complaints in adults include vomiting, chest or abdominal pain, and weight loss.

ENDOSCOPIC FINDINGS

EE has been, and still is, an underdiagnosed condition in many settings, since endoscopic findings are usually much subtler than those seen in esophageal growths or erosive disorders (37). A careful exam is therefore needed that should include biopsy samples from all suspect cases in order to ensure a proper diagnosis (38). From an endoscopic viewpoint EE has a great variety of potential findings (39-41) (Fig. 1). Literature reports include re-

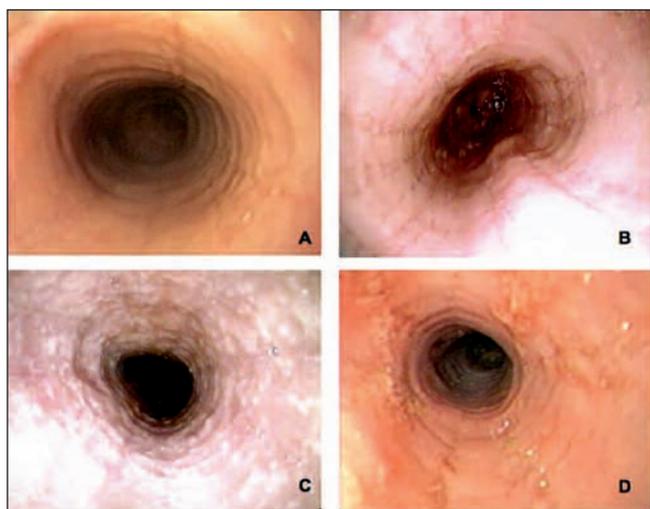


Fig. 1. Several endoscopic aspects of eosinophilic esophagitis. A: Normal-caliber esophagus with longitudinal linear furrows and smooth mucosa. B: Frail-looking, "crêpe paper" mucosa with marked mucosal corrugation. C: The esophageal mucosal surface may be covered in cotton-like exudates mimicking candidiasis, but biopsy finds them to be multiple eosinophil-containing micro-abscesses. D: Reduced-caliber, trachealized esophagus with irregular, cobblestone appearance.

duced esophageal caliber (42) as focal or segmentary stenoses, trachealized esophagus, irregular mucosa, reddish mucosa, whitish elevated papules that resemble candidiasis (43), longitudinal linear furrows (also called esophageal corrugation) (44), changes in esophageal mucosal pattern (45), mucosal frailty (46), esophageal tears (47), and food impaction (11,30,36). A retrospective review of 117 patients with a histological diagnosis of EE showed that the esophagus had been reported normal in up to 24.79% of cases (39), which suggests that changes in this organ's appearance may be subtle enough to be overlooked by an endoscopist not used to this disease. This highly variable range of endoscopic findings may be classified according to two aspects (34): changes in esophageal caliber, which result from motor disturbances, and changes in mucosal surface, which are a consequence of epithelial inflammatory infiltration. The effect of esophageal smooth-muscle contraction manifests as concentric stenoses that block endoscope progression or as simultaneously contracting rings, which are also responsible for food impaction even in the presence of a normal caliber. The various changes seen on the organ's surface translate the different severities of histological epithelial lesions, and a direct correlation between endoscopic severity, histological severity, and eosinophilic inflammatory infiltration density and activation has been reported (34).

HISTOPATHOLOGICAL FINDINGS

The presence of eosinophils in the esophageal epithelium may be seen in many esophageal conditions (48), and of itself defines no particular disease, but should be assessed within the patient's clinical and pathological context. Eosinophilic infiltration in EE involves the entire esophagus, but often in a patchy manner. It is for this reason that a good diagnosis requires multiple biopsies at different levels. Various papers have reported that the density of eosinophilic infiltration is similar in the distal and proximal thirds of the esophagus (49,50), and a good diagnostic strategy involves collecting samples from both these thirds (1). Number of biopsies is relevant for diagnostic sensitivity, as the latter increases with sample number and reaches 100% with 5 biopsy specimens (51).

The most characteristic finding is a high number of eosinophils infiltrating the esophageal epithelium. The usual assessment approach is their count in fields more densely inflamed using an x400 lens (number per high-power field (HPF), x400). However, this measurement is non-standard as the area included in a HPF varies from one microscope manufacturer to the next. The threshold number of eosinophils in diagnosing EE also varies among authors (6,11,52-55), but it is currently accepted that 15 eosinophils/HPF would suffice in the presence of a consistent clinical context when other histopathological

findings are noted (1). Eosinophils may be diffusely distributed throughout the epithelial thickness, but tend to be more numerous in apical strata near the esophageal lumen (50) (Fig. 2). In cases with higher numbers they usually coalesce and make up micro-abscesses (56), which may eventually destroy the superficial epithelium (34). Extracellular eosinophilic granules and major basic protein (MBP) deposition, both extracellularly (57) and within the cytoplasm (30,50,58), may be seen. Micro-abscesses, extracellular deposition of eosinophilic proteins, and positive immunostaining for MBP are findings exclusive of EE that are not seen in GERD (59).

Good biopsies allow the study of other histopathological findings characteristic of EE, including basal layer hyperplasia with acanthosis or presence of proliferative

stratum cells in higher epithelial levels, elongated papillas in the lamina propria, and intercellular edema, reflected by enlarged intercellular spaces. These findings translate a nonspecific, proliferative epithelial response (34), as may also be seen in GERD (60-62).

Subepithelial collagen deposition has been reported within the esophageal lamina propria of pediatric patients with EE to a significantly greater extent *versus* normal conditions and GERD (57,63), which occurs via a mechanism dependent on $TGF\beta$ and its signaling molecule pSMAC2/3, which implies angiogenesis and cellular migration (57). Murine EE models have established that the organ's fibrous remodeling results from specific tissue eosinophilia as induced by interleukin (IL) 5 (64). No data are available regarding the clinical implications of subepithelial fibrosis in EE or its potential reversibility (65), but the rest of histopathological findings usually regress to normal after therapy (Fig. 3).

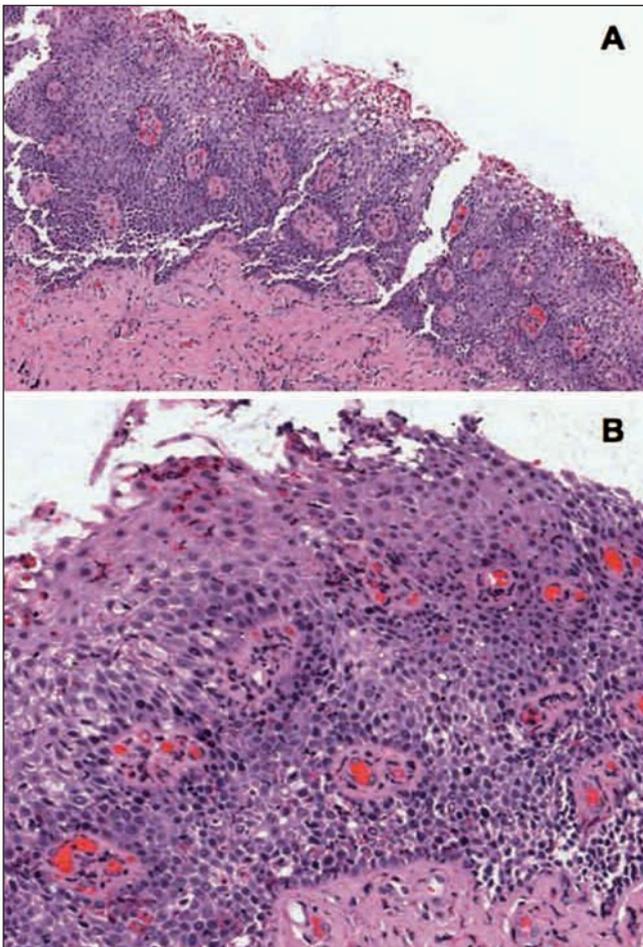


Fig. 2. Histopathological findings characteristic of eosinophilic esophagitis: A: Highly cellular esophageal epithelium with basal stratum proliferation and prominent papillas entering the epithelium from the lamina propria with congestive vessels. Many eosinophils may be found within the full-thickness mucosa, more abundantly in superficial strata by the organ's lumen. In B, described changes may be seen in greater detail, in addition to intercellular spaces, eosinophilic granules, and converging eosinophils that make up micro-abscesses in the esophageal apical surface (hematoxylin and eosin, x200 and x300, respectively).

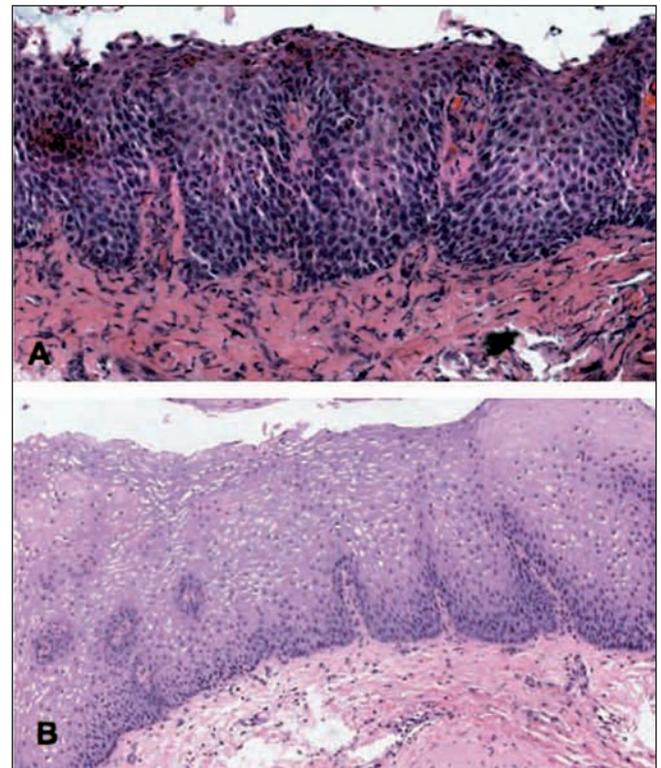


Fig. 3. Images corresponding to this same patient before and after therapy with topical steroids to illustrate changes in the esophageal epithelium: A shows marked epithelial proliferation with basal-cell hyperplasia (more basophilic, polygonal in shape) reaching up to superficial strata, in addition to elongated connective papillas, which appear thicker and hypervascularized. Numerous eosinophils aggregate on the epithelium's surface. After 6 months under treatment with fluticasone propionate (B) the esophageal epithelium exhibits fewer cells and recovered stratification, with basal cells occupying not more than 15% of esophageal thickness, and no eosinophilic infiltration (hematoxylin and eosin, x200).

MOTOR DISTURBANCES IN EE

Eosinophilic infiltration in the human gut is associated with various gastrointestinal motility disorders (66-68). Pediatric patients with EE have been studied with endoscopic ultrasonography, which shows a thickening of the esophageal mucosa and submucosa (69), as well as the muscularis propria (70). Murine models exhibit a dense infiltration of the esophageal muscle with eosinophils (71), which has also been seen in humans (72). A number of motor disorders associated with EE have been reported in the literature, which may be identified with stationary manometry. These include vigorous achalasia (72), diffuse esophageal spasm (73,74), nutcracker esophagus (6,75), high-amplitude peristaltic waves (76,77), tertiary waves (74,78), tone and lower esophageal sphincter functional changes (72,73,79), and nonspecific disorders characterized by low-amplitude, non-transmitted waves with frequent simultaneous sequences (79). Normal manometry recordings have also been described (73,75,77,80,81). Regarding age, disorders characterized by potent, wide waves involving the distal esophagus predominate during childhood; these waves are often concurrent and also develop during sleep and interprandial periods, when the esophagus should remain at rest. On the other hand, the range of motor disorders is wider in adult patients, and includes recordings similar to those of children, but also disorders characterized by low-amplitude, non-transmitted waves in the distal esophagus. Motor disorders predominantly involve the distal two-thirds of the esophagus, which are made up of smooth muscle. Eosinophils themselves have been implicated in the origin of motor disorders; via MBP they influence smooth muscle fibers, since the former is a powerful agonist that can bind the acetylcholine (ACh) M2 receptors governing smooth-muscle function (82,83).

In addition, mast cells in tissue eosinophilic infiltrates (84) also can induce smooth muscle contraction via histamine activity, which induces ACh release and may also alter neuron membrane potential in esophageal plexuses (85), and through their contents in leukotriene C4, another direct stimulant of smooth-muscle contraction.

An association between type of motor disorder and symptom duration has been established in EE (86) in such a way that adults with shorter illness have hyperkinetic disorders similar to those seen in children, whereas those with longer-standing symptoms have hypokinetic manometry recordings. A time progression for this motor disorder has been thus suggested where, following an initial hyperkinetic stage, the esophagus becomes 'exhausted' in a way not unlike achalasia (77,86).

Anyway, evidence suggests that the motor disorder is reversible with treatment once the organ's eosinophilic infiltration is resolved (65,77), which reinforces its functional origin.

DIAGNOSTIC STRATEGY

EE must be suspected for any patient, particularly if young and with a history of allergy, with esophageal symptoms, specifically dysphagia, history of food impaction, or GER-like complaints unresponsive to acid secretion inhibitors. These patients must undergo endoscopy with biopsy collection, at least 5 samples preferentially from the proximal and distal thirds. Samples from the duodenum and gastric antrum should also be collected during endoscopy, while trying to exclude eosinophilic gastroenteritis.

Following the histopathological analysis GER should be excluded as a cause of esophageal eosinophilia (1), albeit the latter condition rarely presents with such dense eosinophilic infiltrates. To this end 24-hour pH-metry recordings should be obtained; should these be pathological or unavailable, esophageal biopsies should be repeated following therapy with maximal-dose proton-pump inhibitors for at least 8 weeks.

At diagnosis the patient should be studied at an Allergy Unit –allergic sensitization, always frequent in these individuals, must be adequately defined, since food and environmental allergens have been implicated in the pathogenesis of EE.

Table I shows the current diagnostic criteria for EE (87).

Table I. Diagnostic criteria for eosinophilic esophagitis (modified from Gonsalves N) (87)

| | Adults | Children |
|-------------------|---|---|
| <i>-Symptoms</i> | Dysphagia Food impaction Heartburn Regurgitation Chest pain Odynophagia | Abdominal pain Heartburn Regurgitation Nausea/Vomiting Dysphagia Failure to thrive |
| <i>-Histology</i> | <ul style="list-style-type: none"> • Esophageal biopsy with ≥ 15 eosinophils / HPF • Normal gastric and duodenal biopsies • 24-hour pH-metry with no pathological GER, or biopsies obtained after 6-8 weeks under dual-dose proton-pump inhibitors | |

HPF: high-power field (400x).

EE AND GERD

EE and GERD share a number of aspects and may look similar on endoscopy, histology, and manometry. In addition, some patients with EE may improve their symptoms with antisecretory medication. Acid reflux does not seem to contribute to EE pathogenesis (88), but the complex pathological links between EE and GERD should be explored (89,90) in order to define whether these two dis-

orders are independent from each other (91), whether GERD-induced damage may cause EE (92), or whether EE may be determinant for GERD, mainly through motor dysfunction at the distal esophagus or lower esophageal sphincter.

TREATMENT OF EE

Dietary management

In 1995 Kelly et al. (8) attained clinical and histological remission in 10 children with GER-attributed eosinophilic esophagitis using elemental diet, but symptoms recurred following the reintroduction of a free diet. In addition to defining esophagitis from severe reflux as dense eosinophilic infiltration, this work established the "gold standard" in the treatment of EE. However, elemental diet has many shortcomings including poor palatability that often requires tube feeding, a high cost, need to closely monitor nutritional deficiency, and unviability for chronic use and adult patients. Hence other alternatives have been attempted including the exclusion of allergic sensitization-related foods, or of potentially allergenic foods, from the diet. Identifying causative food allergens during history taking or via their relation to symptom development is challenging since in most cases inflammation develops within days after exposure due to the delayed hypersensitivity reaction that mediates this condition's pathophysiology. Furthermore, inflammation persists several days after food ingestion, and may result from more than one type of food.

The exclusion of sensitizing foods as seen in allergy tests was successful in a study by Spergel et al. (25), who identified specific foods in 77 of 146 pediatric patients. The disease was adequately managed for 77% of cases, but 10% showed no improvement. A mean of up to 5 foods responsible for EE were identified per patient, and 39 cases worsened after normal diet reintroduction. These results have not been reproduced by other teams, probably due to the fact that allergology methods have variable sensitivity and specificity, mainly because of patch test standardization. It is important, particularly for children, that potential nutrient deficiencies be avoided, since food restriction may become extensive; the participation of a nutrition specialist is recommended.

The third dietary strategy is the suppression of foods considered allergenic. Its initial application in a series of 35 children with EE included the exclusion of 6 products from the diet (milk, soy, eggs, wheat, peanuts, walnuts, fish) regardless of sensitization (93). Following this 34 patients improved or got rid of their symptoms while eosinophil numbers in epithelial infiltrates significantly decreased (from 80.2 to 13.6/HPF). A study in adults using this same strategy yielded partial results (94), with symptom improvement in only 30% of cases, and incom-

plete histological regression. Reasons accounting for these differences include that adult EE seems related to airborne allergens rather than inhalants. To conclude, while an empirical exclusion of foods is easy to implement, it might not eliminate a food necessary for remission, or may be too strict and include unnecessary exclusions.

Drug therapy

Drug therapy for EE is problematic in several ways -- unavailability of drugs specifically approved for this condition, a chronic course that discourages long-term drug administration, or absence of definite long-term prognostic data on EE and its potential complications to avert the risk of prolonged systemic treatment. Furthermore, none of these therapies has proven adequate to modify the course of disease in the long run, or to prevent complications from arising (e.g., fibrous esophageal stenoses) (13). However, symptom frequency and severity, the risks of repeated endoscopic procedures, and quality of life involvement requires a number of therapies, as follows.

—*Proton-pump inhibitors (1)*: acid suppression in EE is necessary to rule out GERD as a cause of esophageal eosinophilia when pH-metry is unavailable, or pathological, and also in patients with concomitant EE and GER (91). Thus, while acid secretion inhibitors should not be considered specific for EE, they may contribute to relieve associated symptoms in some individuals.

—*Systemic corticosteroids (prednisone)*: since 1996 several experiences show their effectiveness after oral administration (78,95,96) at doses of 0.5 to 1.5 mg/kg/day. However, the disease recurs within months after discontinuation, which, together with adverse effects from chronic use in pediatric patients, discourages their use in favor of safer alternatives.

—*Topical corticosteroids*: fluticasone propionate is most commonly used given its characteristics, which render it particularly suitable for EE -- low systemic bioavailability through the inhaled route (negligible through the gastrointestinal route, < 1%), liver first-pass effect approaching 99%, non-absorbable by the esophageal mucosa, instability in an acid medium. Since first described in EE (97), both in children (53,75,98-101) and adults (11,28,34,50,77,102,103) it has shown a therapeutical effectiveness similar to systemic steroids (104), while adverse effects are kept to a minimum. This treatments's main shortcoming is its difficult administration -- it is usually available in devices for inhalation, and for EE must be swallowed after applying it on the tongue. Hence successful treatment greatly depends on adequately instructing the patient on how the drug should be used. A liquid fluticasone preparation for nasal use is available in our country that may be easier to use in EE. The pa-

tient must be instructed not to eat or drink for at least 30 minutes following administration, otherwise the steroid would be washed into the stomach; a mouthwash should also be recommended after use to prevent oral candidiasis. Difficulties for adequate administration to pediatric patients may be overcome by using viscous budesonide (57,101), which adequately covers the entire esophagus, and is safe and effective. Fluticasone doses range from 176 µg/day in children up to 4 years of age to 1,000 µg/day in adults (in two administrations) for 6 to 12 weeks. As for budesonide, commonly used doses are 1-2 mg/day in 8-12 mL once a day.

—*Mast-cell stabilizing substances* (disodium cromoglycate) had been put to good use in EG for their resistance to gastric acidity (105). In EE, Liacouras et al. (52) used up to 100 mg daily (in four doses) in a series of 14 children with EE, and observed no clinical or histological improvement at 1 month after treatment onset, hence the drug cannot be recommended for this disease.

—*Anti-leukotrienes*: Montelukast has been tried in a series of 8 patients with EE (106) at very high doses (> 100 mg/day). After several weeks 7 reported symptom remission, and the rest symptom improvement. However, in no case did esophageal histology return to normal. Another study that measured gene expression levels for cysteinyl-leukotrienes in the esophageal epithelium found them similar in children with EE and normal controls (107). While Montelukast does not seem to achieve remission in this disease, we still do not know its efficacy in maintaining corticoid-induced remission.

—*Azathioprine/6-mercaptopurine*: a study in three adult patients with steroid-dependent EE (108) who received immunomodulation with purine analogs showed symptom and eosinophilic infiltration remission during therapy (from 3 to 8 years) with no need for steroids. Upon discontinuation the disease recurred in two patients.

—*MepolizumAb* is a humanized monoclonal antibody against IL-5, a TH2 cytokine that plays a key role in the proliferation, differentiation, survival, and activation of eosinophils in chronic allergic airway conditions (109) and in EE (110,111), both in humans (112) and animal models (113). Its use has been successful in EG (114) and hypereosinophilic syndrome (115), and more recently in EE (116). A double-blind, randomized, placebo-controlled clinical trial is now ongoing in adult patients with EE, where mepolizumAb has demonstrated good tolerability and a highly significant reduction in eosinophil numbers both in the blood and esophagus, with no changes induced on other inflammatory cells or on the expression of other proinflammatory cytokines in the blood (117). OmalizumAb (anti-IgE) (118) has not proven effective in EE.

Endoscopic management

Esophageal food impaction is the complaint most commonly leading to a diagnosis of EE in adult patients

(34), and often requires urgent management with endoscopy. Patient age, previous repeat impactions, and potential allergic history should be considered for EE suspicion. The exam should focus on the presence of stenoses or esophageal rings, and of the above-mentioned mucosal changes; also, if EE is suspected, biopsy samples should be collected from the organ's mucosa, even if its appearance is considered normal.

Endoscopic dilations are a common therapy for fibrous or rigid stenoses secondary to long-term inflammation healing involving the gut mucosa. Esophageal stenosis dilation in EE has been used by several authors in the management of this condition (40,46,100,119), and provided immediate symptom relief (120,121). However, various complications have also been reported with this technique, more frequently in EE *versus* other conditions, including perforations (122-124), hematomas (125), and unusual tears, the latter particularly common during rigid endoscopy (47). Therefore, endoscopic dilation is a risky therapy in these individuals (126) that should be avoided first-line until eosinophilic infiltration can be effectively ruled out, and reserved for symptomatic patients where medical treatment failed (127).

EE management controversies

Multiple controversies exist on the management of EE, both in children and adults, that currently have no definite scientific answer. EE, as other allergic conditions, is a chronic condition where eosinophilic infiltration and symptoms usually recur after treatment discontinuation. Adult (128) and pediatric (52) series followed up for 10 or more years show a chronic course in most patients, and progressive disease in severe cases; spontaneous resolution is rare. Whether disease persists in all children until adulthood is unknown -- many adults report symptoms since childhood (65), whereas others have a limited duration. EE has been considered a risk factor for esophageal perforation from vomiting or endoscopic procedures, and may predispose to fungal or viral infection (123). While it does not seem to limit life expectancy, it does substantially affect quality of life, even though many patients eventually learn to live with their symptoms. The clinical relevance of long-term epithelial fibrous remodeling is unclear, but patients with longer-standing symptoms may have reduced response to therapy (128).

All this leads to consider maintenance therapy for EE, similar to other allergic conditions such as bronchial asthma, but definitive data on their risks and cost is as of yet unavailable.

Now we know that EE symptoms may fluctuate spontaneously, or even stay in stand-by even with persistent eosinophilic infiltrates in histological studies. A consensus reached by an expert committee on EE (1) has recom-

mended treatment for histology even in the absence of symptoms, due to the potential risks posed by esophageal fibrosis and remodeling, and stenosis formation.

The established scarce predictability of symptoms on inflammation has led to consider endoscopy with biopsy collection in the management and follow-up of patients, as well as in the evaluation of food withdrawal or introduction effects. Therefore, endoscopic exams under sedation should be carried out in all these patients.

While most children and adults with EE have atopy and experience a number of other allergic manifestations (asthma, rhinoconjunctivitis, eczema, etc.), there is also a small group of subjects with EE symptoms and histopathology in the absence of other atopy complaints. In these allergy tests yield no positive results, and no response to elemental diet is seen among children (32). All these patients successfully respond to topical steroids, but disease recurs upon their discontinuation. Whether all these patients have the same disease, or whether EE pathophysiology is one throughout the complete clinical spectrum is unclear (16), but several cytokine gene expression profiles have now been demonstrated in patients with EE (112). Anyway, allergy should be adequately studied in all patients, since food or environmental allergies triggering the condition should be identified; adequate exposure control would be a cheap, effective, safest therapy, regardless of drug therapy needs.

CONCLUSIONS

EE is a chronic (both clinically and histologically) disease with an incidence much higher than previously thought, and that may substantially compromise patient quality of life. Adequate management requires cooperation by gastroenterologists, allergists, and pathologists, as it represents an emerging diagnostic and therapeutic challenge in view of its growing epidemiology. It should be suspected in any patient with refractory GER symptoms, or with dysphagia and food impaction, most particularly in young males with a history of allergy. Diagnostic suspicion should prompt biopsy collection even from a normal-looking esophagus. Diet therapy and allergen exposure control are most desirable; otherwise, topical steroids are currently the first-choice therapy for this disease.

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