

Invited Review

Eosinophilic Oesophagitis: Epidemiology, Clinical Aspects, and Association to Allergy

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ABSTRACT

Eosinophilic oesophagitis is characterised by age-dependent symptoms mimicking gastrooesophageal reflux disease, a distinct endoscopic appearance and a histological picture with extensive infiltration of eosinophils in the oesophageal mucosa. Eosinophilic oesophagitis is more frequently seen in males, and patients often belong to the paediatric or adolescence age groups. The exact prevalence of eosinophilic oesophagitis is unknown, but it has been suggested that the United States has a higher prevalence than Europe. Several treatment algorithms have been suggested, including elemental diets, oral steroids, inhaled (swallowed) steroids, and leucotriene receptor antagonists. Detailed information on the eosinophilic inflammatory processes in the oesophageal mucosa was initially obtained from animal models, in particular with regard to the

role of interleukin-5 and the chemokine eotaxin-1 in eosinophilic recruitment. Studies have suggested a cytotoxic effect of eosinophilic degranulation products on nerve fibers in the gastric/intestinal mucosa, implicating a direct effect of allergic inflammation on gastrointestinal motility. Human studies recently have emphasized the role of eotaxin-3 and identified a single nucleotide polymorphism probably related to disease susceptibility. *JPGN* 45:281–289, 2007. **Key Words:** Eosinophilic oesophagitis—Prevalence—Interleukin-5—Food allergy—Eotaxin—Gastrooesophageal reflux—Oesophagitis. © 2007 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

INTRODUCTION

A limited physiological number of eosinophils are present in the gut as a natural part of host defence. The oesophagus is, however, normally devoid of eosinophils. During the last decade, eosinophilic oesophagitis (EE) has been recognised as a separate entity distinctly apart from both eosinophilic gastroenteritis and oesophageal eosinophilia induced by gastrooesophageal reflux disease (GERD) (1–3). Eosinophilic oesophagitis is characterised by reflux-like symptoms, but especially dysphagia and food impactions. The characteristic endoscopic appearance, a histological picture with massive accumulation of eosinophils in the oesophageal epithelium, normal pH monitoring results, and the ineffectiveness of antireflux treatment separate EE from GERD. The paradigm of an allergic basis for oesophageal eosinophilia was first

introduced by Kelly et al (4) in 1995. The authors identified a group of 10 children characterised by GERD-like symptoms and a pronounced oesophageal eosinophilia unresponsive to classic GERD treatment, including proton-pump inhibitors and surgical fundoplication. A significant reduction in the eosinophilic infiltration was observed after treatment with an amino acid–based diet in this admittedly limited study group.

The aim of this review is to summarize the current knowledge of the epidemiology and the clinical and pathophysiological aspects of EE, with special attention directed at apparent differences in prevalences, the association with airway allergy, and efficacy of treatment modalities in EE.

DEFINITION

No uniform definition of EE exists. As a general assumption, EE may be defined as the presence of more than 20 eosinophils per high power field (HPF) (magnification $\times 400$) in biopsies from any part of the oesophagus. Additional findings such as basal-zone hyperplasia and elongation of the rete papillae may supplement the diagnosis (5). If lower numbers of eosinophils are

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observed, then it may be difficult to differentiate between EE and GERD at the histological level, as discussed later.

EPIDEMIOLOGY

Two epidemiological findings are characteristic of EE. First, a clear sex difference is observed with 66% to 91% male patients in published series (2,6–10). No clear explanation for this observation has been identified. Second, EE seems to be more frequent in younger subjects, with the majority of identified patients being children or adolescents.

Increasing Prevalence or Increased Awareness?

During the last decade, increasing numbers of EE cases have been identified, especially in the United States. A population-based study found a prevalence of 1/10,000 in a midwestern community, representing a 4-fold increase over a 4-year period (11). A recent Australian publication has confirmed an increase in the prevalence of EE there. Paediatric oesophageal biopsies from 1995, 1999, and 2004 were reevaluated. The prevalence of children diagnosed with EE (in this study, >24 eosinophils per HPF) increased from 0.05/10,000 to 0.89/10,000 during this 10-year period. Interestingly, not only the number of children but also the severity of the inflammation increased, with higher numbers of eosinophils and increased frequency of basal-zone hyperplasia and elongation of the rete papillae observed during the study period (5). Only limited data are available from Europe. Straumann (2) observed an increasing prevalence among adults in Switzerland; during a 16-year period the prevalence figures increased from 2 to 23/100,000 patients. No data are available for the paediatric population from European centres.

Markowitz et al (7) investigated which fraction of patients referred for suspicion of GERD finally was diagnosed with EE. From a population of 346 mixed paediatric/adult patients with chronic GERD symptoms, 51 (15%) were identified as EE patients. The authors applied strict diagnostic criteria for EE, which included the presence of >20 eosinophils per HPF in oesophageal biopsies, normal oesophageal pH monitoring, and lack of response to proton-pump inhibitor treatment.

The increasing frequency of EE, in particular in the United States, could be explained by increasing prevalence, increased awareness, or both. Provided that an increased prevalence has developed during the last decades, such a development may be explained by differences in food-antigen exposure, other environmental influences, or genetics. A development within genes within a time span of a few decades seems unlikely. With regard to EE, 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 EE. 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 in the United States. Up to one third of patients with severe EE may have a normal-appearing oesophagus at endoscopy (10), thus EE is diagnosed only if biopsies are performed (12). If the patient undergoes endoscopy because of suspicion of GERD, then a normal-appearing mucosa may not be evaluated histologically and the condition could be diagnosed as negative endoscopy reflux disease/nonerosive reflux disease (NERD). In this case, treatment likely would be initiated with antireflux drugs such as proton-pump inhibitors (13).

Given that a proportion of EE patients display airway sensitisation, an increase in EE may additionally be part of a general increase in the prevalence of asthma and allergy as documented in the International Study of Asthma and Allergies (14). In conclusion, only limited information is available on the prevalence of EE in different parts of the world. Prospective, population-based studies based on clinical, endoscopic, and allergological patient characterisation are needed.

ASPECTS OF PATHOGENESIS

Several cytokines and chemokines have been shown to be of importance for the initiation and maintenance of the eosinophilic inflammation in the oesophagus. Comprehensive reviews have been published (15–17). In addition to their regulatory role, the eosinophils exert important effector functions (18). The Th2 cytokine interleukin (IL)-5 is the single most important factor for the release of eosinophils from the bone marrow into the bloodstream. Several cytokines and chemokines are able to regulate eosinophilic accumulation in the gastrointestinal (GI) mucosa; however, IL-5 and the chemokine eotaxin-1 display a high degree of eosinophilic selectivity in animal studies. Interleukin-5 was shown to be a crucial factor for oesophageal-eosinophilic accumulation in an experimental model of food allergy (19). Eotaxin-1 is expressed in the GI tract at physiological conditions and is of importance for maintaining baseline levels of GI eosinophils (20). Upregulated eotaxin-1 levels have been observed in eosinophilic GI disorders (21).

Intestinal mucosal damage induced by eosinophils is mediated by at least 4 different granular proteins: major basic protein, eosinophil cationic protein, eosinophil peroxidase, and eosinophil-derived neurotoxin. Besides various cytotoxic effects, major basic protein and eosinophil peroxidase both display a direct effect on smooth muscle tone (22). A functional importance of the interaction between eosinophils and nerve fibres has been indicated in a mice model of GI eosinophilia. Hogan et al (21) observed a Th2-associated eosinophilic inflammation involving the oesophagus, stomach, and small intestine

after sensitisation to ovalbumin. Morphologically, damaged enteric nerve endings in close proximity to eosinophils were observed by electron microscopy. A loss of intracellular organisation of the nerve fibres indicated axonal necrosis and thereby disruption of GI motility induced by the eosinophils. However, it is unknown whether these observations may also be present in human tissue. A possible role of eotaxin-1 in cow's milk-sensitive reflux disease in children was reported in a study including 9 cow's milk-sensitive GERD patients (23). The expression of eotaxin-1 was upregulated as assessed by immunohistochemistry and a semiquantitative grading system because eotaxin-1 depots were found in the basal and papillary epithelium of the oesophagus (24).

Straumann (25) evaluated the activity patterns and the cytokine profile of oesophageal eosinophils in 8 patients with EE and a control group with functional dyspepsia. Oesophageal eosinophils from the EE patients stained positive for the activity marker CD25 compared with duodenal eosinophils. No CD25⁺ eosinophils were observed in the controls. No differences were noted between EE and controls with regard to the population of CD25⁺ eosinophils in duodenal biopsies. In addition, the population of oesophageal eosinophils was characterised by a higher expression of the Th2 cytokines IL-4, IL-5, and IL-13, a finding that was confirmed by Gupta (26), who compared mRNA expression of interferon- γ , IL-5, and eotaxin-1 from the inflamed mucosa of EE patients with controls. These observations have been used to explain the pathogenesis of the oesophageal-ring formation often observed in patients with EE. Mann et al (27) hypothesized that upon antigen exposure, oesophageal mast cells increase histamine levels and subsequently induce accumulation of eosinophils in sensitised individuals. Secondly, eosinophilic chemotactic factors result in further eosinophilic accumulation and degranulation. Acetylcholine induced by histamine may result in smooth-muscle contraction of the circular layers in the oesophageal wall. Indeed, mast-cell activation and increased mucosal histamine levels have been observed in experimental models of oesophagitis (28,29). In addition, mast-cell mediated oesophageal shortening in in vitro experiments could be inhibited by the mast cell stabiliser disodium cromoglycate (30,31). However, counteractive mechanisms may operate as the proinflammatory cytokines IL-1 β and IL-6 also secreted from activated mast cells were recently shown to reduce oesophageal circular contraction by inhibition of acetylcholine release from the myenteric plexus in a cat model of oesophagitis (32). Interestingly, increased levels of mast cells were observed in the oesophageal mucosa, strengthening the hypothesis of a possible association of mast cells, histamine, and oesophageal-ring formation. A recently published study by Blanchard et al (33) analysed the potential role of eotaxin-3 in the pathogenesis of EE. Using a genome-wide microarray expression analysis, a

specific transcript signature was observed in biopsies from EE patients despite clinical differences such as sex, age, and subtype of EE (allergic vs nonallergic). Compared with healthy controls and patients with GERD, the gene-encoding eotaxin-3 was the most highly induced gene. In addition, the oesophageal levels of eotaxin-3 messenger RNA correlated not only with number of eosinophils but also with numbers of mast cells in the mucosa. The levels of eotaxin-1 were not significantly different from those in patients with GERD. The changes of eotaxin-3 were seen for both allergic and nonallergic EE, indicating that different subtypes of EE may have a common underlying disease mechanism, presumably the production of increased levels of eotaxin-3 in the oesophageal mucosa. An eotaxin-3-positive population of mononuclear epithelioid cells was identified in the epithelial layer of the oesophageal mucosa, and increased serum levels of eotaxin-3 were seen. Importantly, this study also identified a single-nucleotide polymorphism leading to disease susceptibility.

In conclusion, detailed information on the eosinophilic process in the oesophagus has been obtained from animal models. Characterisation of the cytokines of eosinophilic inflammation, and especially of the role of eotaxin-3 in the human oesophagus, is emerging.

GEOGRAPHY OF SENSITISATION: IS THE ALLERGIC AIRWAY THE NEW "LORD OF THE OESOPHAGEAL RINGS"?

It has been that speculated that EE is a new GI manifestation of food allergy. However, it seems a paradox that the target inflammatory site is the organ in which the food antigen enters and exits rapidly, and with the allergen in its structurally most preserved form. It has been suggested that the place of sensitisation is the duodenum, and that the eosinophilic accumulation is the result of the eosinophils homing back to the oesophagus (34). Studies of experimental eosinophilic disease in mice have challenged this paradigm of sensitisation occurring in the GI tract. Mishra et al (35) showed that mice sensitised with *Aspergillus* in the trachea had severe accumulation of eosinophils, not only in the lungs but also in the oesophagus. In addition, free eosinophilic granules and basal-zone hyperplasia were observed in the oesophageal mucosa. Attempts to sensitise the animal by oral or intragastric methods did not result in eosinophilic infiltration in the oesophagus. The association in animal models between the allergic airway and eosinophilic oesophagitis may be of clinical significance, as illustrated by the large proportion of patients with EE who suffer from bronchial asthma and allergic rhinoconjunctivitis. Case reports have shown a temporary improvement and recurrence of eosinophilic inflammation and EE symptoms with seasonal variations in pollen concentrations (36). Higher numbers

of eosinophils were observed in proximal oesophageal biopsies from patients ($n = 38$) sensitised to grass pollen and suffering from allergic rhinitis and/or bronchial asthma when compared with patients with GERD (37). However, the mean number of eosinophils of $5.5 (\pm 7.3)$ per HPF did not qualify for the diagnosis of EE, but indicated that airway sensitisation may play a role in the pathogenesis of EE. No studies have evaluated the possible relationship by simultaneous biopsies from both mucosal areas. Recently, it was suggested that sensitisation resulting in oesophageal inflammation may also occur via the skin (38). Using an experimental mice model, it was shown that both wild-type and genetically manipulated mice exposed to the antigen by the epicutaneous route primed the oesophagus for marked eosinophilic infiltration after airway challenge with the same antigen. The importance of this observation in humans with eczema remains to be evaluated.

The animal experiments and clinical observations presented above raise the question whether the oesophagus is an innocent bystander or the target organ for the sensitisation process. Likewise, it is unknown if swallowed airway mucus in sensitised individuals is sufficient to induce oesophageal eosinophilia. It has been suggested that the eosinophil is the new lord of the oesophageal rings. Whether the true lord actually is the allergic airway needs to be evaluated in future EE protocols, with rigorous identification of both airway and gastrointestinal sensitisation and preferably simultaneous identification of the inflammatory patterns and cytokine profiles in both areas.

TYPE OF SENSITISATION IN PATIENTS WITH EOSINOPHILIC OESOPHAGITIS

Sensitisation may be identified by dietary challenge, preferably as double-blind placebo-controlled food challenge (39) (Fig. 1). Spergel (40) prospectively evaluated several food antigens and type of sensitisation in 26 patients with EE. Positive skin-prick tests were observed in 19 patients and positive skin-patch tests in 21 patients. Fourteen patients were positive for both diagnostic tests. The most common food antigens identified were: cow's milk (13), egg (12), soy (5), wheat (5), beef (5) and rye (5). Patients were instructed to eliminate all test-positive foods and then reintroduce a single food at a 5-day to 7-day interval and evaluate reoccurrence of EE symptoms. By this algorithm a mean of 3.6 causative foods was identified. Pure immunoglobulin E-mediated reactions were seen in 4 of the 26 patients; non immunoglobulin E-mediated in 5, and mixed-type reaction in 15. After elimination diet, a reduction from a mean of 55.8 eosinophils per HPF to 8.4 eosinophils per HPF occurred at repeated biopsy. The authors concluded that T-cell-mediated reactions were responsible in the subset of patients with EE who had negative skin-prick tests and

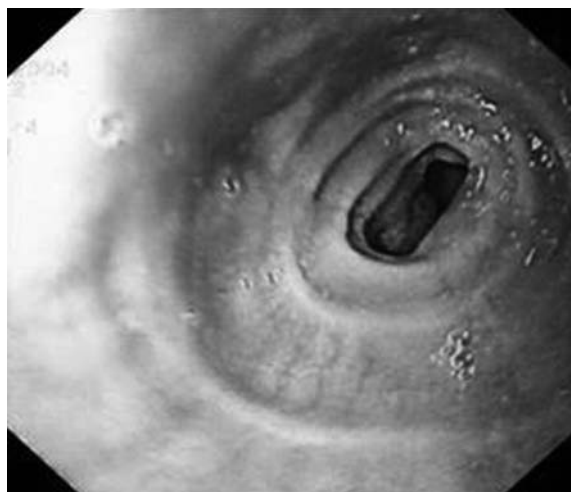


FIG. 1. Endoscopy of eosinophilic oesophagitis in a 25-year-old male with symptoms of pyrosis and food impactions for several years before diagnostic evaluation. Additional symptoms of allergic rhinitis were apparent during the grass-pollen season. Upper endoscopy revealed the classic picture of a ringed oesophagus with multiple concentric rings appearing toward the lower oesophageal sphincter. In addition, whitish plaques are seen representing eosinophil microabscesses localised in the superficial mucosa. The pH monitoring was normal. Histology displayed a dense eosinophilic infiltrate of 55 eosinophils per high power field ($\times 400$).

positive patch tests. The possible diagnostic value of skin-patch tests in children with predominantly gastrointestinal symptoms of food allergy also has been suggested previously (41), but confirmatory studies specifically in EE are needed.

CLINICAL ASPECTS

Symptoms

The symptoms of EE may mimic gastrooesophageal reflux disease with dyspeptic symptoms, abdominal pain, chest pain, heart burn/pyrosis, regurgitation, and vomiting. Symptoms are typically age-dependent with non-specific symptoms in infants and younger children such as failure to thrive, vomiting, nausea, feeding refusal, and abdominal pain (42). Dysphagia to solid foods and food impaction in the oesophagus are characteristic for EE in older children and adults (43–45). Guajardo (8) found food impactions to be the only symptom which appeared significantly more frequent among 39 patients with EE compared to 57 patients with eosinophilic gastroenteritis. Recently, Desai et al (44) reported that 17 of 31 adult patients (55%) presenting with food impactions harboured more than 20 eosinophils per HFP in oesophageal biopsies. Thirteen of the 17 patients were treated with proton pump inhibitor at the time of biopsy. Immunohistochemistry revealed increased amounts of CD8+ T-cells and deposits of eosinophilic major basic protein in the oesophageal

epithelium interpreted as activation of the eosinophils at the time of food impaction.

Cheung (6) retrospectively analysed 42 children referred for evaluation of dysphagia. Twenty-one children (50%) displayed oesophageal eosinophilia. Compared to the group of 21 children without eosinophilia, the EE group was characterised by a significant male predominance, history of allergy, and food impactions. No differences regarding pH monitoring and motility patterns were observed between the groups.

Dysphagia and food impactions may be caused by motility disturbances or overt strictures. Motility disturbances are induced either by an increased thickness of the oesophageal wall as reported by endoscopic ultrasound (46) or by interference of the normal propagating motility patterns by secretions of eosinophilic granules and their toxic products as major basic protein and eosinophilic cationic protein (21). The majority of patients with EE have additional allergic manifestations as bronchial asthma, allergic rhinitis, and eczema, or have a family history of atopic disease (2,42,47,48). Because of the overlapping symptoms, EE may be mistaken as GERD, but lack of symptom control is frequently seen after treatment with acid suppression (7,13) and the pronounced eosinophilia usually persists at post-treatment follow-up endoscopy/biopsy.

ENDOSCOPIC FINDINGS

Several endoscopic features are characteristic of EE. Vertical rings and whitish nodules are the most frequently observed changes. Occasionally, the endoscopic appearance of the oesophageal mucosa in EE may be normal or characterised by only minimal changes (10). However, as many as 93% of EE patients display one of the features that have been identified as characteristic for EE (49). It should be emphasised that eosinophilic oesophagitis based upon the histological diagnosis may present with no or minimal macroscopic changes, illustrating the importance of biopsies from patients with classical symptoms, especially dysphagia and food impactions despite normal endoscopic findings (50).

Vertical Lines/Ringed Oesophagus

The endoscopic appearance of EE is characterised by concentric vertical rings in the oesophagus (51–55) (Fig. 2). The inflammatory process may proceed to fibrosis, resulting in regular stricture formation or long-segment stenosis often recognised as a small-calibre oesophagus (49,56,57).

Ring formation may be so pronounced that the term trachealization has been used for this corrugated oesophageal picture (3). Gupta (54) found a high correlation between the endoscopic appearance of vertical lines and presence of eosinophils on histological examinations of

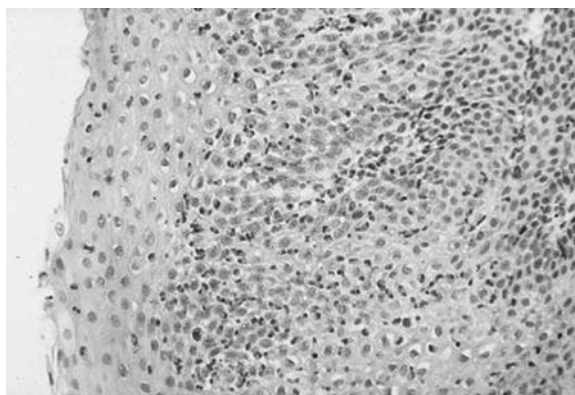


FIG. 2. Histology of eosinophilic oesophagitis. A 12-year-old boy presented with gastrooesophageal reflux disease-like symptoms of upper abdominal pain and pyrosis for 2 years at time of evaluation. Endoscopy visualised a normal-appearing oesophageal mucosa. The pH monitoring showed a slightly elevated acid-reflux index. The histology of the oesophageal biopsies showed a dense eosinophilic infiltration of the mucosa of the oesophagus stretching toward the lamina propria. Skin-prick test and specific immunoglobulin E were normal. Skin-patch test was positive for cow's milk. Suspicion of sensitisation to cow's milk was confirmed by a double-blind placebo-controlled food challenge, with symptoms reappearing only when tested with cow's milk and not during placebo (soy milk) in this diagnostic set-up. Symptoms and oesophageal eosinophilia resolved during diet that eliminated cow's milk.

oesophageal biopsies. The radiological equivalent of these rings was documented in barium studies by Zimmerman (58), strictures in 10 of 14 EE patients. In 50% of cases, the multiple ringlike strictures were noted not only in the lower but also in the middle and upper parts of the oesophagus.

White Nodules

Accumulation of white nodules/plaques may resemble a fungal infection. Biopsies from these areas identify the histological correlate of the whitish areas as eosinophilic microabscesses with a dense accumulation of eosinophils located superficially in the oesophageal mucosa (1).

Fragile Mucosa/Longitudinal Tears

The mucosa of EE patients may be unusually fragile, with lesions appearing after minimal trauma, such as introduction of the endoscope. Lesions may be seen as diffuse mucosal bleeding or longitudinal tears. A characteristic feature is extensive longitudinal tears appearing after even gentle dilations of EE-mediated strictures, or merely the endoscopy itself (1).

ENDOSCOPIC ULTRASOUND

Endoscopic ultrasound has been used to evaluate the deeper layers of the oesophageal wall. Increased thickness of the total oesophageal wall was observed in children with

EE (46). This observation indicates that not only the superficial mucosa, but also the deeper muscular layers of the oesophageal wall, may be affected by the eosinophilic infiltration.

HISTOLOGY: HOW MANY EOSINOPHILS ARE TOO MANY?

The oesophagus is normally devoid of eosinophils (59,60). In the remaining part of the GI tract, a small physiological number of eosinophils is present as part of the regional host defence (61). Evaluation of the number of eosinophils in biopsies should always be performed in light of this background. EE is characterised by a dense accumulation of eosinophils in the superficial layers of the oesophageal wall and, in some cases, formation of an eosinophilic microabscess.

Traditionally, eosinophilia is quantified as the number of eosinophils per HPF, selecting the single most densely infiltrated area for evaluation. Liacouras (47) advocated evaluation of several HPFs and then calculating a mean value. We recently reported that the size of biopsies from the paediatric oesophagus might vary by a factor of 20. We presented an alternative computer-assisted method for evaluation of allergic inflammatory cells in upper gastrointestinal biopsies based upon the total biopsy area (62). We observed several discrepancies between the HPF and the computer-assisted method in a study of inflammatory cells in cow milk-sensitive reflux disease (63). At present, no consensus exists on the number of eosinophils needed to establish the diagnosis of EE. A cutoff limit of >20 eosinophils per HPF is widely used, although some authors use lower limits (42). Ruchelli et al (13) evaluated the efficacy of GERD treatment with H_2 blocker plus prokinetics relative to the degree of eosinophilic inflammation in the oesophagus. A significant difference in the numbers of eosinophils was observed in 3 clinical groups classified according to treatment response: good response (mean eosinophilic count per HPF [MEC] = 1.1), treatment relapse (MEC = 6.4), and treatment failure (MEC = 24.5). A threshold $MEC \geq 7$ was found to have a predictive value of 86.1% of treatment failure and a $MEC < 7$ to have a predictive value of 85% for reflux-treatment success. Thus, the density of the eosinophilic infiltration may assist the diagnostic differentiation between eosinophilia secondary to GERD and eosinophilia due to EE. A general interpretation may be that <10 eosinophils per HPF in the distal part of the oesophagus indicates inflammatory changes secondary to GERD, 10–20 eosinophils per HPF may be regarded as the grey zone where further diagnostic procedures or repeated endoscopy may be necessary, and >20 eosinophils per HPF is indicative of EE. In contrast to GERD-induced inflammation of the distal part of the oesophagus, the eosinophils in EE may be more pronounced in the proximal oesophagus, underscor-

ing the importance of multiple biopsies (42,44). In addition to eosinophilic accumulation, increased thickness of the basal zone as a criteria for oesophagitis also is found in biopsies from EE patients (6,33). Characterisation of oesophageal eotaxin-3 expression may provide further information in the differentiation between GERD and EE in the future (33).

TREATMENT

The efficacy of EE treatment should preferably be documented not only by relief of symptoms, but also by reduction of the eosinophilic-inflammatory infiltrate in the oesophageal mucosa as evaluated by repeated biopsies.

Elimination Diet

Elemental diet was introduced as a treatment modality of EE by Kelly et al in a study population of 10 children (4). A 6-week period of elemental diet resulted in almost complete ablation of the eosinophils from the oesophagus at post-treatment biopsy. These findings have been confirmed in the study by Markowitz (7), who identified 51 EE patients using strict diagnostic criteria. All patients received elemental diet (Neocate1+, Nutricia, Zoetermeer, NL) plus water, with only 1 type of fruit as a supplement. Improvement was noticed in 49 of the 51 patients. A significant reduction in EE symptoms such as vomiting, abdominal pain, heartburn, and dysphagia was noted after a mean period of 8.5 days. A highly significant reduction in the mean number of eosinophils per HPF was observed from the pretreatment (33.7 eosinophils/HPF) to the post-treatment (1.0 eosinophils/HPF) biopsy. In conclusion, elemental diet may act as a logical treatment of EE.

Systemic Steroids

The effect of systemic steroids was studied by Liacouras et al (47) in a population of 20 children with a mean age of 5.9 years characterised by presence of more than 15 eosinophils per HPF in the oesophageal biopsies. Patients with eosinophilic gastroenteritis were excluded. Cases with eosinophilia secondary to GERD were excluded by oesophageal pH monitoring. Thirteen patients became asymptomatic and 6 showed marked improvement after a 4-week treatment period of methylprednisolone 1.5 mg/kg twice daily. At follow-up biopsy, the number of eosinophils per HPF decreased from 34.2 to 1.5. At 12-month follow-up, 10 patients remained asymptomatic and only 2 patients required a second course of systemic-steroid treatment. In conclusion, systemic steroids may be used in refractory cases, but several courses may be required over time.

Inhaled Steroids

Topical application of steroids at the oesophageal mucosa has been used to avoid the potential side effect of systemic steroids. Faubion et al (64) treated 4 boys (ages 12–13 years) with severe EE (>50 eosinophils per HFP) by swallowed fluticasone (220 µg/puff, 4 puffs) or beclomethasone (42 µg/puff, 1 puff) given twice daily for 6 weeks. The treatment was given by an inhaler without a spacer, and the patients were instructed to swallow after inhalation. The 4 patients experienced improvement in EE symptoms within 1 week after initiation of treatment. Teitelbaum (65) showed an effect of inhaled fluticasone in a study of 11 children with EE. A significantly increased number of CD1a antigen-presenting cells in the oesophageal mucosa was observed before treatment compared to controls. In addition to a reduction in eosinophils, the numbers of CD3- and CD8-positive T-cells also were significantly reduced at follow-up oesophageal biopsy. A topical viscous budesonide suspension may be used in neurologically impaired children who are not able to perform an inhaler puff-and-swallow sequence (66). Further characterisation of the effect of fluticasone on the immunopathological features in EE was published by Noel and colleagues (67). Pre- and post-treatment biopsies from 20 children with EE were analysed for numbers of CD-8-positive T-cells, papillary lengthening, and proliferation of the oesophageal-mucosa basal layer as assessed by Ki-67. Post-treatment biopsies showed a significant reduction of CD-8 T-lymphocytes, papillary lengthening, and basal-zone thickness. Interestingly, all skin prick-negative patients responded to fluticasone treatment, whereas the immunoglobulin E-sensitised individuals were more refractory to treatment, possibly due to lack of effective elimination of the causative food antigen from the diet. The efficacy of swallowed fluticasone propionate recently has been documented in a double-blind placebo-controlled trial. During a 3-month treatment period, the fluticasone group (n=21) significantly decreased symptoms and achieved histological remission at follow-up biopsies compared to the placebo group. In addition, significantly reduced numbers of mast cells and CD8+ T-lymphocytes were observed (68).

In conclusion, topical steroids may be used before systemic-steroid administration and may be supplementary to dietary treatment.

Leucotriene Receptor Antagonist

The tissue damage induced by eosinophil and mast-cell degranulation is partly mediated by products of the arachidonic metabolism such as the cysteinyl leucotrienes. Leucotriene receptor antagonists only have been evaluated in small patient series. Attwood et al (69) treated 8 adult patients with EE in an open-label study with the Cys LT₁

selective antagonist Montelukast. Improvement in swallowing function was observed in 6 of the 8 patients. The positive effect of Montelukast also was suggested in a small uncontrolled study of 8 children (70). The use of leucotriene receptor antagonists in EE is promising, but needs evaluation in larger controlled protocols with repeated biopsies to document reduction of eosinophilic inflammation.

Future Treatment Modalities

Major contributors in the eosinophil-inflammatory process are the cytokine IL-5 and the chemokine eotaxin-1. A therapeutic effect of monoclonal antibodies toward IL-5 has been suggested in case reports of treatment of hyper-eosinophilic syndromes, including a case of EE treated with anti-IL-5 (mepolizumab). Larger multicenter studies will be needed to address both efficacy and safety concerns before general acceptance of this treatment regimen. Increased levels of IL-13 have been observed in the inflamed oesophageal mucosa of patients with EE, suggesting modulation of IL-13 as a future treatment option (50). In animal studies on BALB/c mice, a significant decrease in oesophageal eosinophilia was observed with a monoclonal IL-13 antibody, possibly limiting both the systemic and local Th2-cell response. Likewise, an anti eotaxin-3 monoclonal antibody may be the target for future research strategies in the treatment of EE.

Treatment Strategy/Protocol

A practical treatment strategy for EE was published by Ngo and Furuta (71). Initially, an allergological diagnostic work-up is performed addressing both immunoglobulin E and non-immunoglobulin E mechanisms, and identified food allergens are excluded from the diet. If no causative food antigen can be identified, an elemental diet is introduced. If an elemental diet proves ineffective to control EE symptoms or is not tolerated, topical steroids may be used by an inhalator puff-and-swallow sequence. Systemic steroids are reserved to treat resistant cases. Symptom relief aside, clinical efficacy of the initiated treatment should be evaluated by repeated oesophageal-mucosal biopsies in order to document the disappearance of eosinophilic infiltration.

CONCLUSIONS

Eosinophilic oesophagitis is a newly described disease entity with an estimated increase in prevalence during the last decade in the United States and more uncertain data in other parts of the world. Experimental animal models have provided an understanding of the major immunological events led by IL-5 and eotaxin-1 to this localised eosinophilic-inflammatory process. Recently, the discovery of the role of overexpression of eotaxin-3 in human studies

has challenged the IL-5/eotaxin-1 paradigm. Interestingly, an association with airway sensitisation has been observed, which is not yet as fully understood. A consensus for the description of endoscopic and histological findings will be advantageous. Clinical effect of elimination/elemental diets and immune-modulating treatments has been suggested from a series of studies of limited sample size.

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