

Eosinophilic Esophagitis- Clinical Management in Adults

Kouklakis S Georgios*, Vradelis D Stergios and Dellaportra Erminia

Professor of Gastroenterology Democritus University of Thrace, Greece

*Corresponding author: Kouklakis S. Georgios, Professor of Gastroenterology Democritus University of Thrace, Greece, Tel: 00302551351003; E-mail: gkouklak@med.duth.gr

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Abstract

Eosinophilic esophagitis (EoE) represents a chronic, immune-mediated esophageal disease, characterized clinically by symptoms related to esophageal dysfunction, histologically by eosinophilic infiltration of esophageal mucosa and endoscopically by a range of abnormalities. EoE is increasing in prevalence and predominantly affects children and young males, with a racial predilection of the patients being Caucasian. The relationship between EoE and gastroesophageal reflux disease (GERD) can be complex, since their clinical and pathologic features may overlap. Furthermore, an entity that can be considered a subtype of GERD or EoE is the proton pump inhibitor-responsive esophageal eosinophilia (PPI-REE). PPI-REE emerged from the observation that some patients who appeared to have EoE would have a clinical and histologic response to PPI treatment. Currently, upper endoscopy with esophageal biopsies is the only way to diagnose EoE. Fifteen eosinophils/high-power field (hpf) are considered a minimum threshold for the diagnosis of EoE, since the disease is isolated to the esophagus and other causes of esophageal eosinophilia are excluded. Patients commonly have concurrent allergic diatheses, especially to food. The therapeutic options of EoE include: chronic elimination diet, topical corticosteroids and esophageal dilation. We review the latest approach to clinical diagnosis and management of EoE.

Keywords: Chronic; Immune-mediated; Eosinophils; Eosinophilic

Epidemiology

The prevalence and incidence of EoE are variable depending on the study design but they are rapidly increasing as the disease is globally endorsed in daily clinical practice [8,9]. Estimated overall prevalence in general population is between 40 and 90/100,000 persons in most studies from America, Australia and Europe [10-17]

The prevalence of EoE in those who undergo upper endoscopy highly depends on the indication. The overall prevalence for any indication ranges from 2.4% up to 6.6% [18-20]. If the indication is dysphagia then the prevalence is up to 23% [21-23], and this rate rises up to 63% if an urgent endoscopy for food bolus impaction is performed [24,25]. Given that is not a common practice to take biopsies during urgent endoscopy for food impaction the aforementioned rate is probably underestimated and this highlights the importance of EoE as a major cause of food impaction. In those patients who underwent endoscopy for upper gastrointestinal symptoms, EoE is established in between 5-16% [18].

EoE can affect any age, but it is more prevalent in children and young males and its peak is from 35 to 45 years old age [17]. Male to female ratio is 4:1 [12,26] but the reason is still unknown for this male predominance. A racial discrepancy has also been identified as EoE is more prevalent in whites [27].

The incidence of EoE ranges from 6 to 13 cases/100,000 persons [15,28].

Natural History

EoE is a chronic unremitting disease [29], but does not influence life expectancy. It is restricted to esophagus and does not progress to other parts of gastrointestinal tract. As a matter of time, EoE

Introduction

Eosinophilic esophagitis (EoE) is a clinicopathologic entity that was first described in an individual patient in late 1970's [1,2], but it was only during the last decade that has emerged as important cause of esophageal dysfunction, dysmotility and consequent symptoms. Normally, the squamous epithelium of esophagus is devoid of eosinophils and is an exception, as every other part of gastrointestinal tract contains eosinophils [3]. EoE has been reviewed extensively elsewhere [4-6] and an overview of clinical management in adults is given here only to provide a manual in daily clinical practice.

Definition-Diagnostic Criteria

EoE is a chronic, immune-mediated clinicopathologic disease characterized clinically by upper gastrointestinal symptoms, histologically by eosinophilic infiltration of esophageal mucosa and endoscopically by a range of abnormalities, depending on age and chronicity [4,5]. Recent guidelines set the following criteria, that are required for diagnosis: symptoms related to esophageal dysfunction; eosinophilic-predominant inflammation localized to the esophagus, with at least 15 eosinophils/high-power field (hpf) in esophageal mucosal biopsies (distal and proximal), and exclusion of secondary causes of esophageal eosinophilia, including proton pump inhibitor-responsive esophageal eosinophilia (PPI-REE). To exclude PPI-REE, patients must be placed on PPI treatment prior to confirming the diagnosis of EoE. Those with esophageal eosinophilia who respond have PPI-REE instead of EoE. A response to treatment (dietary elimination; topical corticosteroids) supports, but is not required for, diagnosis [7].

transforms from the inflammatory phenotype in children to fibrostenotic phenotype in adults [30,31].

Clinical Presentation

The clinical presentation of EoE varies on patient's age and there are two major clinical phenotypes depending on this. The inflammatory -predominant phenotype (children) progresses to the fibrosis-predominant phenotype (adults) [28,32,33] and these phenotypes provide insights to the natural history of EoE.

The typical patient with EoE is a young male with a history of atopy (75%) and symptoms of dysphagia to solids and food bolus impaction [34]. In many cases symptoms are non-specific and cause diagnostic delay and the patient's eating behavior that is associated with esophageal remodeling contributes to that [35]. A recent study demonstrated that the median diagnostic delay from onset of symptoms to index diagnosis was 6 years [33]. The following symptoms are those that a patient with EoE can present:

Dysphagia

Dysphagia to solids is the commonest symptom presenting in 25% to 100% of cases and it can be chronic and/or intermittent in nature [12,22]. Esophageal remodeling, which is the process of fibrosis throughout the chronic course of the disease appears to be a principal cause of dysphagia [36]. Dysphagia is also attributed to esophageal dysmotility that is related to EoE. The most common disorders of esophageal motility seen in EoE are weak peristalsis and failed peristalsis [37].

Food Impaction

As already mentioned, EoE is the most common cause of food impaction among patients who undergo urgent endoscopy, comprising more than 50% of cases. Patients with food impaction usually report past episodes and modify their eating behavior in order to alleviate their symptom. For instance they report drinking considerable amounts of liquids, chewing excessively their food or even walking or jumping during meals [24,25,38].

Heartburn/Acid Reflux not Responsive to Medical Treatment

Symptoms of reflux like heartburn and acid regurgitation are prevalent in EoE patients as they present from 24% up to 50% [39]. EoE is the cause in 1%–8% of patients with PPI-refractory reflux symptoms [40]

Chest Pain

Chest pain unrelated to swallowing presents in 13% to 36% of EoE patients [35]. Inflammation, GERD and acid hypersensitivity have been implicated to pathogenesis of this symptom [4].

EoE is also strongly associated with atopic diseases such as asthma, atopic dermatitis, allergic rhinitis and sinusitis and food allergies, with this relationship first reported in children, where up to 80% report atopy and 30% present with peripheral eosinophilia.

EoE may be revealed by oesophageal complications such as spontaneous perforation which might be transmural (Boerhaave's syndrome) or partial as intramural tears or deep lacerations during

endoscopy. Fortunately, these complications are rare and have been described only as clinical cases in the literature.

Endoscopy

Upper endoscopy is required to evaluate the clinical symptoms of dysphagia and EoE, assess for other possible causes, and take esophageal biopsies. Typical endoscopic findings of EoE are the following:

Esophageal rings: Rings can be either fixed (previously referred to as esophageal trachealization or corrugation) or transient (sometimes termed felinization).

Narrow caliber of esophagus: This finding mostly demonstrate chronicity of the disease.

Focal esophageal strictures: Strictures can be located in the proximal, middle, or lower third of the esophagus

Longitudinal furrows: Furrows are grooves in the esophageal mucosa that run parallel to the axis of the esophagus.

White plaques or specks: Punctate white spots on the esophageal mucosa that can be confused with esophageal candidiasis. They may represent eosinophilic microabscesses.

Decreased vascularity: The normal mucosal vascular pattern is lost.

Crêpe-paper mucosa: This finding represents mucosal friability, where the mucosa tears by the mere passage of the endoscope.

A new endoscopic classification system has been proposed. Its name is EoE endoscopic reference score (EREFS) and validates exudates, rings, oedema, furrows and strictures [41].

Many of the aforementioned endoscopic findings occur together, but are not all seen in every patient with EoE. A substantial proportion of EoE patients (10-33%) have no mucosal lesions during endoscopy. Consequently, if biopsies are not taken, the disease will be missed [42]. Furthermore, the endoscopic findings of EoE are not pathognomonic, so this emphasizes the importance of obtaining esophageal biopsies when EoE is suspected clinically. If they are present are suggestive of EoE, but biopsy sampling is always mandatory even in a normal appearing esophagus, as already mentioned. Because inflammatory changes in EoE are often patchy, it is recommended that 2-4 biopsies should be obtained from both the proximal and distal esophagus to maximize the likelihood of detecting esophageal eosinophilia. It is also reasonable to take biopsies from the areas of abnormal findings. Biopsies should also be taken from the antrum and/or duodenum to rule out other causes of esophageal eosinophilia in all patients with gastric or small intestinal symptoms.

Histopathology

There is a dense eosinophilic infiltration of the esophageal epithelium, which can be stained by hematoxylin and eosin. The least number of eosinophils per high power field (HPF) required in a mucosal biopsy is 15, for someone to consider the diagnosis of EoE [4,43]. Unfortunately, the typical endoscopic features of EoE have a poor predictive value for a diagnosis of EoE, with only 38% of patients who had typical endoscopic features suggestive of EoE meeting the histologic criteria for EoE on midesophageal biopsies [22]. There is a marked variability in the density of eosinophilia in biopsies taken from different levels of the esophagus, with levels from the distal esophagus being numerically greater than those from the proximal esophagus.

The latter can be attributed to the more frequent tissue injury in distal esophagus comparing to proximal. Additionally, it has been demonstrated that the sensitivity of one biopsy specimen was 55% and increased to 100% with five biopsy specimens [44].

Another issue that needs to be addressed is the patchy distribution of eosinophils that makes necessary the acquisition of esophageal biopsies from multiple sites [45].

Differential Diagnosis

There secondary causes of esophageal eosinophilia that need to be excluded: Gastroesophageal reflux disease (GERD), PPI-REE, eosinophilic gastroenteritis, Celiac disease, Crohn's disease, Achalasia, Connective tissue disease and hypereosinophilic syndrome.

There is a substantial overlap between EoE and GERD. Half of the patients with GERD present with eosinophils in tissue samples and the burden of eosinophils correlate well with endoscopic grading of the disease [46,47] and is thought to represent a normal response to esophageal mucosal injury [48]. As a result, even very high eosinophil counts cannot distinguish the two diseases. It is clear that there are some patients who have coexisting EoE and GERD and that the relation between the two conditions is complicated.

Additionally, there was an observation that some patients who appeared to have EoE would have a clinical and histologic response to PPI therapy. This phenomenon has been termed PPI-REE. At this time, the entity is considered distinct from EoE, but not necessarily a manifestation of GERD. It seems to be a subtype of GERD or EoE variant [49]. To exclude PPI-REE, patients with suspected EoE, a high dose PPI trial (20-40 mg twice daily of any of the available agents for 8 weeks) should be given followed by endoscopy with biopsies. Several studies reported response to PPIs treatment in up to 2/3 (75%) of cases as there is a speculation that PPIs may have anti-inflammatory or barrier-healing properties that contribute to resolution of esophageal eosinophilia [50,51]. If a patient responds to this regimen (clinical, endoscopic, and/or histologic response), then additional clinical evaluation should be performed to determine if GERD was the cause of the esophageal eosinophilia. This may include ambulatory pH monitoring test. If a patient has persistent symptoms of EoE and there are still at least 15 eos/hpf on esophageal biopsy, then EoE can be diagnosed.

Treatment

Over the last 15 years, a lot of research has been made to develop an effective strategy for treatment of EoE. Main goals of treatment of EoE are improvement in clinical symptoms and resolution of esophageal eosinophilic inflammation. First line treatment includes drugs and diet, whereas endoscopic dilation is reserved to those with strictures.

Corticosteroids (Systemic and Topical)

Steroids are the mainstay of treatment and improve symptoms and histology of EoE. Additionally, they reduce fibrosis and esophageal remodelling [52] Systemic steroids (prednisone, methylprednisolone) rapidly resolve symptoms and histology, but since reduced or withdrawn EoE recurs. Systemic side effects restrict their use to patients with severe symptoms that require rapid resolution, like emergent cases, such as dysphagia requiring hospitalization or dehydration or when topical steroids are not effective.

Topical corticosteroids like fluticasone or beclomethasone in a multi-dose inhaler (MDI) in a daily dose of 1760 mcg/day that are swallowed, appear effective to reduce patient's eosinophilia and symptoms [53]. Oral viscous or swallowed nebulized budesonide have shown efficacy in a dose of 2 mg/day. To obtain a viscous form, budesonide solution (1 mg/2 ml) is mixed with sugar substitute (5 packets of sucralose). Patients should be advised to puff the inhaler into the mouth during a breath hold and then to swallow it. After taking these drugs, patients should avoid eating or drinking for at least 30-60 min. There have been no studies comparing the efficacy of fluticasone to budesonide, but a recent study examined two topical formulation of budesonide, showing that the oral viscous form was more effective than the nebulized swallowed one. Treatment duration with swallowed topical steroids is usually 6-12 weeks. In children, randomized trials comparing fluticasone to prednisone and to placebo showed an approximately 50% complete and 95% partial response after treatment of 1-3 months. However, studies showed that EoE reappeared usually within 9 months in the majority of patients after steroid discontinuation. A potential side effect that needs to be taken into account is that, 10-35% of treated patients with topical steroids presented with esophageal candidiasis [54-56].

Other Agents

Novel agents have been studied on a limited basis in EoE but their efficacy is not established. Several biologics (mepolizumab, reslizumab, Omalizumab and Remicade) tested with no success and they are not recommended [57,58].

Montelukast, a leukotriene inhibitor was ineffective. There is a lack of controlled trial in patients with EoE. In a case series of adults treated with high doses of montelukast, there was symptomatic but not histologic response in 12 patients, hence in a study of 11 adult patients, montelukast was not effective for maintaining a steroid-induced remission [59].

Although mast-cell inhibitors have a theoretical place in the treatment of EoE, cromolyn sodium was used for 4 weeks in 14 children who failed to demonstrate either symptomatic or histologic improvement.

The immunomodulators 6-mercaptopurine and azathioprine were used in three adult patients with steroid-dependent esophageal eosinophilia with resulting symptomatic and histologic remission [60].

None of these medications is recommended for routine use due to potential side effects. When patients do not respond to a topical or systematic administration of steroids (after dose escalation or longer treatment), a non-medical treatment of EoE is recommended, such as dietary elimination or endoscopic dilation.

Dietary Elimination

There are three strategies of dietary therapy. The first is a total allergen-free elemental formula, composed of only amino acids, medium chain triglycerides and simple carbohydrates. The second one is a targeted elimination diet where foods are removed based on allergy testing (skin prick testing or patch testing). The third one is the six-food elimination diet, where the six most highly allergenic food groups, egg, milk, wheat, soy, nuts and seafood, are removed from the diet. All these three diets have showed symptomatic and histologic resolution in EoE patients [61-65]. Meta-analysis demonstrated that elemental diets were effective for 91% of patients, non-directed diets

for 72%, and allergy test-directed diets for 46% [66]. The duration of the treatment is usually 4-8 weeks. Then a period of reintroduction follows once remission has been achieved.

When selecting dietary approach as treatment for a patient with EoE, it is important to consider consultation with an allergist and nutritionist. This helps that patients are having their nutrition requirements met. A major advantage of diet, when compared to steroids, is that offers long-term remission instead of steroids that discontinuation causes recurrence of EoE. Diet also improves fibrosis and delays esophageal remodelling [67].

Endoscopic Treatment

Esophageal dilation, either by balloon or bougienage technique, may be used in symptomatic patients with strictures, who do not respond to medical or dietary treatment. The role of dilation as primary treatment is controversial and should be individualized. It has no effect on esophageal inflammation. With hydrostatic balloon dilation inspection of the underlying esophageal mucosa is easy without having to reintroduce the endoscope. On the other hand, bougie dilation with a wire-guided system is usually used to dilate multiple and long strictures.

During dilation, small increases in diameter over the sessions are advocated, because of the known fragility of the esophageal mucosa in EoE. If the regular upper GI endoscopy of adults passes without resistance (diameters from 9 to 10 mm), then the initial size of the dilator should be just above this. An esophageal diameter of 15-18 mm after dilation in EoE is reported to be enough for relief of dysphagia. Risks of dilation in EoE are post-dilation chest pain (up to 75% of patients), bleeding and esophageal perforation (up to 8%) [68-70].

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