Recent advances in the recognition and management of eosinophilic esophagitis

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The incidence and recognition of eosinophilic esophagitis is increasing. Pathophysiological understanding of eosinophilic esophagitis is improving and an immunological reaction to ingested food is likely to play a significant role. Patients present with dysphagia and food bolus obstruction. Both histological and endoscopic criteria have been developed and validated. Dietary therapy, topical steroid therapy, proton pump inhibitors and endoscopic dilation are the main approaches to therapy; however, novel targeted therapies are being developed. Among the food items commonly implicated are wheat, dairy, nuts, soy, shellfish and eggs. A multidisciplinary approach to management in dedicated clinics may yield the best results.

Key Words: Endoscopic findings; Eosinophilic esophagitis

DEFINITION AND EPIDEMIOLOGY

Eosinophilic esophagitis (EoE) is a comparatively recent newcomer to the field of gastroenterology, with the first case described in literature by Landres et al (1) in 1978. Since then, its recognition as a clinically relevant and potentially manageable disorder has increased, first in pediatric and, more recently, in adult gastroenterology. EoE in adults is defined clinically by symptoms of esophageal dysfunction, including dysphagia, reflux and food impaction (2,3). Histologically, it is defined by an eosinophil-predominant inflammatory response (4). EoE was initially believed to be a rare disorder of childhood and has only been described in the adult literature since 1993. Since that time, however, likely due to both increased recognition and increasing incidence (5), the number of cases has surged dramatically. Dellon et al (6) conducted a large study involving >35 million individuals in the United States, with estimates of overall adult prevalence of EoE to be 56.7 per 100,000. Other smaller studies have reported adult prevalences of anywhere from 23 per 100,000 in a Swiss study (7) to 400 per 100,000 in a smaller study from Sweden (8). Regardless of the true number, there is little argument that the prevalence of EoE is significantly greater than anyone had realized even a decade ago, and that it will represent an expanding clinical challenge in the coming years. It is, therefore, important to optimize and standardize the recognition and management of EoE in adult gastroenterology practice.

PATHOGENESIS

While its pathogenesis remains largely under investigation, EoE is believed to be primarily an allergy-mediated disorder in response to ingested or inhaled antigens. It is not, however, a traditional immunoglobulin (Ig) E-mediated allergic response as indicated by the lack of utility of traditional cutaneous allergy testing and the lack of resolution in patients treated with anti-IgE therapies (9,10). It is not clear why these allergens produce a pathological response; however, there are theories proposing an impaired epithelial barrier in EoE patients because there is a demonstrated downregulation of the cell adhesion protein DSG-1 in active EoE that partially resolves with treatment (11).

This impaired barrier may facilitate the overexposure of antigen to professional antigen-presenting cells in the esophagus. The allergic stimulus triggers a T-helper cell 2-mediated allergic response in the esophagus, with the release of interleukin (IL) 13 and IL4 (12,13) – cytokines that act as mediators of several other allergic disorders such as asthma and atopic dermatitis. IL13 and IL4 then cause the esophageal epithelium to secrete eotaxin-3, a powerful chemotractant that causes eosinophilic and mast cell migration to the esophageal epithelium (14). Another powerful chemotractant, thymic stromal lymphopoietin, is found at higher concentrations in biopsies of EoE patients and its deletion in murine models eliminates EoE, thus supporting its role in the disease (15,16).

Chronic eosinophilic inflammation and inflammation leads to tissue remodelling with deposition of fibrin, epithelial hyperplasia, abnormal angiogenesis and hypertrophy of the muscularis propria (17-21). IL13 and IL4 are also believed to play a direct role in remodelling by activating fibroblast and stellate cells and causing increased expression of matrix proteins (13,22). Chronic remodelling results in the endoscopic findings characteristic of EoE including corrugated esophagus, linear furrowing and stricture formation (23-25). There is controversy regarding the relative involvement of IgG4 versus IgE (26).

CLINICAL PRESENTATION

Clinically, EoE presents with symptoms consistent with esophageal dysmotility and mechanical obstruction. Dysphagia, reflux and food impaction are the most common presenting complaints for adolescents and adults, while children can present with nonspecific features such as abdominal pain or failure to thrive (4). Several studies have shown that typical endoscopic features, when combined with clinical symptoms, other risk factors, such as an atopic history, can often discriminate EoE from mimics such as reflux esophagitis (27,28). In a meta-analysis by Kim et al (29), at least one endoscopic abnormality (including esophageal rings, strictures, narrow-calibre esophagus, linear furrows, white plaques, and paller or decreased vasculature) was observed in 92% of patients with EoE, the most common of which were esophageal rings and linear furrows.
DIAGNOSIS
While there are certainly suggestive characteristics endoscopically, traditional diagnosis still relies on histology of biopsies obtained at endoscopy. Before the landmark review of EoE by Furuta et al (30) in 2007, there was little consensus as to the precise diagnostic parameters for the disease. The Furuta review delineated clear criteria including histology showing >15 eosinophils per high-power field in ≥1 biopsies, clinical symptoms and the exclusion of gastroesophageal reflux disease (GERD) as the cause for eosinophilia. Evolving knowledge has led to evolving guidelines, with the most recent changes in 2011 recognizing the uncertainty around EoE by establishing a new clinically distinct entity known as proton pump inhibitor-responsive EoE (PPI-REE). This new category recognizes that there are patients with EoE-like disease, as opposed to GERD, which does respond well to PPI therapy (4). This uncertainty arises from the fact that, despite clear diagnostic criteria, the distinguishing line between EoE and GERD is not always clinically very clear. Numerous studies have demonstrated an eosinophilic infiltrate in GERD patients and, in fact, because of the huge prevelance of GERD, the majority of patients with an eosinophilic infiltrate are likely to have GERD rather than EoE (31). Adding to this uncertainty is the recognition that EoE disease can be patchy and individual biopsies may miss affected areas (32). In fact, biopsy technique is another evolving area of research. In terms of location of biopsy, earlier reports suggested focusing on the distal esophagus. Current practice, however, suggests obtaining biopsies from the middle and distal esophagus to minimize confusion with reflux esophagitis. The ideal number of biopsies remains unclear, with a study by Gonsalves et al (33) demonstrating sensitivities of biopsies from 55% to 100% for one and five biopsies, respectively. A recent study by Nielsen et al (34) suggests four biopsies from the mid and distal esophagus with no increased sensitivity beyond six biopsies.

The reason many clinicians are uncomfortable with diagnostic uncertainty in EoE is that it has been shown to be a progressive disease, with often irreversible fibrotic and stenotic changes that accumulate in untreated patients. Delays in diagnosis have dire consequences for patients, as shown in a study by Schoepfer et al (35) in 2013. Percentages of patients suffering from stricture disease rose from 17% when diagnosed within two years of onset to >70% when there were delays in diagnosis of >20 years. Another study by Dellon et al (36) showed the risk of fibrostenotic disease doubling for every 10 years of disease progression.

The typical findings at endoscopy of EoE include esophageal rings, linear furrows, exudates, pallor, loss of vasculature, mucosal fragility and strictures (36). In 2011, a study by Hirano et al (37) investigating the intra-observer validity of various endoscopic features, fixed rings/strictures, exudates, furrows and edema had the best predictive value for an eventual EoE diagnosis. These endoscopic features are more likely to be present in patients with definite EoE compared to patients with GERD. Additionally, confocal laser endomicroscopy (CLE) has been shown to be useful in the diagnosis of EoE, with studies demonstrating a high sensitivity and specificity for the identification of eosinophilic infiltration (38, 39).

Figure 1) A High-definition endoscopy showing linear vertical furrows with subtle circumferential rings. B to D iSCAN (Pentax, USA) virtual chromoendoscopy better define linear furrows and characterize the white exudate as mild disease. E and F iSCAN virtual chromoendoscopy characterizes the rings as severe disease. G Confocal laser endomicroscopy showing dilated intercellular spaces with microabscess and leakage of fluorescein. H and I Hematoxylin and eosin stain (original magnification x200 – 400) showing large number of intraepithelial eosinophils as well as basal cell hyperplasia, spongiosis and microabscesses.
findings have become the hallmarks of EoE and should prompt biopsies and further diagnostic workup during routine endoscopy. However, some of the features may be subtle and easily missed and, in 5% to 10% of patients, the endoscopy may be described as normal. Obtaining multiple biopsies from at least two locations, such as proximal and distal esophagus, is essential in any patient with suspected EoE, regardless of endoscopic findings. A validated EoE endoscopic reference score has recently been described, which may be used in clinical trials as well as in clinical practice to longitudinally follow-up patients with EoE. It is known as the EoE endoscopic reference score (EREFS), the acronym also reflects the major components of the score: exudates, rings, edema, furrows and strictures (37).

Narrow-band magnifying endoscopy may also enable visualization of the fine capillary patterns and other subtle abnormalities that can help in the diagnosis of EoE (38). The appearances of EoE on confocal endomicroscopy has been described (39). Given the patchy nature of involvement, endoscopy with biopsies may miss the involved areas and confocal endomicroscopy may provide further help in localizing the disease and obtaining targeted biopsies. In addition, a tethered capsule confocal endomicroscopy has been described, which may help in the diagnosis and follow-up of EoE (40) (Figure 1).

**THERAPY**

As the recognition of EoE and understanding of its pathophysiology develops, so do novel therapeutic approaches. To date, the cornerstones of treatment have been exclusion diets and topical swallowed steroids along with PPIs for PPI-REE and endoscopic dilation for strictures or rings. Exclusion diets rely on the assumption of ingested antigens triggering an eosinophil-predominant inflammation and their use has been mostly studied in the pediatric population. Several variations of dietary therapy have been evaluated including amino acid-based formula diets, the ‘six food’ exclusion diet (dairy, eggs, peanuts, soy, wheat and shellfish) and diets tailored to individual allergens; all have shown degrees of success (9,41-43). These diets appear to have more utility in pediatric populations, in which adherence to strict diets are more feasible. One of the problems of exclusion diets are the strategy for reintroduction of food items without requiring esophageal biopsies. In adult EoE, swallowed topical steroids are the current treatment of choice. Fluticasone inhalers are commonly used as a swallowed medication at doses from 440 µg to 880 µg twice daily. Preparations of viscous budesonide are equally effective (44) but are often a challenge to obtain. In randomized controlled trials, topical steroids have been shown to be effective in reducing both the clinical symptoms and endoscopic changes in EoE (45). New evidence suggests they may also reverse the remodelling process caused by chronic inflammation (46). Unfortunately, numerous studies have shown that the benefits of treatment stop with discontinuation, usually within several months (45). Strictures may not resolve on medical therapy alone and esophageal dilation may be necessary to improve dysphagia rapidly. Esophageal dilation does not carry any higher risk of perforation than esophageal dilation of benign strictures in the absence of EoE.

While exclusion diets are difficult to maintain and the prospect of chronic steroids often unattractive for both prescribers and patients, focus has shifted to novel therapies. IL5 and IL13 have been the subject of targeted, biologic-based therapy for EoE, with the former having undergone more clinical trials. As previously outlined, IL5 is one of the major cytokines implicated in the pathogenesis of EoE. To date, four studies have investigated anti-IL5 molecules (mepolizumab and reslizumab) as therapies for EoE. Although all studies demonstrated a reduction in intraepithelial eosinophil counts, a significant clinical improvement was not demonstrated (47-51). Experimental anti-IL13 antibodies have been developed for use primarily in asthma and inflammatory bowel disease; however, one clinical trial is investigating its role in EoE (Efficacy and Safety of QAX576 in Patients With Eosinophilic Esophagitis). Results of this study are not yet published.

**REFERENCES**

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