Historical Aspects of Eosinophilic Esophagitis: From Case Reports to Clinical Trials

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Abstract
Eosinophilic esophagitis (EoE) is a clinicopathological condition characterized clinically by symptoms of esophageal dysfunction in the absence of acid reflux, with typical endoscopic findings and eosinophilia on biopsy. This article looks into the historical clinical recognition and description of EoE, in particular clinical manifestations, natural history, and epidemiology. Additionally, the evolution of endoscopic recognition and development of clinical trials are described: EoE is an isolated disease of the esophagus, although it is associated with other antigen-driven diseases such as asthma, rhinitis, and atopic dermatitis. After initial case reports which were mostly not typical of the disease state now described, the first case series were described in 1993 and 1994 in adults, and 1995 in children. Although rarely seen before 2000, the disease is now commonly recognized. Randomized clinical trials have now been performed on topical steroids, and on biological agents targeted against IL-5, IL-13, and other mediators. Therapy with dilatation may be best guided by measures of compliance and distensibility. Work is needed on biomarkers of the disease’s severity and progression, and predictive indexes of complications. EoE is a relatively new disease of increasing importance. It represents an important diagnosis in patients with upper gastrointestinal symptoms and must be considered in all patients with dysphagia where the diagnosis is not certain and in all patients who have an assumed diagnosis of reflux but are not responding to standard reflux therapy.

Introduction

The identification of a distinct disease termed esophageal eosinophilia or eosinophilic esophagitis (EoE) with its own clinical characteristics (dysphagia in adults and regurgitation and feeding difficulties in young children) and separate from reflux injury or other known diseases was described in the early 1990s. Prior to this, descriptions of esophageal eosinophils were single case reports and associated with a variety of disorders without any specific disease pattern. This paper will describe the milestones in the development of our understanding of EoE including the initial case report, the first case series, the first description of natural history, and the development of therapies. There have been relatively few randomized clinical trials, but the development of international consensus guidelines has been an important step which has helped to standardize the diagnostic and therapeutic approach.

In 1978, Landres et al. [1] reported an isolated case of vigorous achalasia in a patient with marked hypertrophy and eosinophilic infiltration of esophagus. They conclud-
ed that this was a variant of eosinophilic gastroenteritis which predisposed to esophageal motor disorder. This case had no other features of what we now recognize as EoE. It is still unusual to discover any excess of eosinophils in patients with achalasia or other defined motor disorders of the esophagus.

In 1981, Picus and Frank [2] reported a case of a 16-year-old boy with progressive dysphagia for 1.5 years. Endoscopic findings were suggestive of multiple 1-mm nodular filling defects in the esophagus in an area of stricture with dilatation above. Radiology showed a luminal narrowing, wall rigidity, and high circulating eosinophil count. The authors assumed it was a variant of eosinophilic gastroenteritis. Similarly, Münch et al. [3] (1982) and Matzinger and Daneman [4] (1983) both described isolated cases of esophageal eosinophilia with dysphagia in patients with assumed eosinophilic gastroenteritis. In 1985, Feczko et al. [5] reported 3 cases of eosinophilic infiltration of esophagus, with 2 of the patients showing eosinophilic gastroenteritis. Two out of 3 patients developed esophageal stricture secondary to submucosal fibrosis. The author did not clarify any etiology and assumed reflux was involved, but in retrospect these were probably EoE. Lee [6] in 1985 reported eosinophilic infiltration in esophageal mucosal biopsy in 11 patients with average age of 14.6 years – these patients had reflux symptoms and their eosinophil density was low. In retrospect, these were probably patients with gastroesophageal reflux disease (GERD).

In 1993, Attwood et al. [7] reported 12 adults with dysphagia, normal pH monitoring, and dense esophageal eosinophilia (>20 eosinophils/high-power field [HPF]). Importantly, control patients with proven GERD had a mean of 3.3 eosinophils/HPF in their esophageal mucosa. Seven patients had food hypersensitivity, and all required advanced intervention (dilatation and/or steroids in 1 case) for resolution of symptoms. The following year, Straumann et al. [8] described a series of 10 patients with acute recurrent dysphagia seen over a 4-year period who showed discrete endoscopic changes and high concentrations of epithelial esophageal eosinophils treated with systemic steroids and antihistamines. The first publication in children was by Kelly et al. [9] in 1995, and they identified 10 children who were diagnosed on clinical and histological grounds to have EoE. Six out of those 10 had been subject to antireflux therapy without any symptomatic improvement. Two of these patients had already received fundoplication, and all responded well to amino acid formulas, suggesting an allergic etiology. The characteristics in pediatric EoE appeared to reflect greater amounts of regurgitation and failure to thrive, while the typical presentation in adults with EoE was dysphagia and food impaction.

Following these initial case series, very little progress was apparent in the literature for the next 8–10 years until the description in 2003 of the chronic nature of the natural history of EoE. Straumann et al. [10] described the longest follow-up of 30 adults with EoE [22 men, mean age: 40.6 years (range: 16–71)]. The presenting symptom was almost exclusively dysphagia with food impaction, and diagnosis was delayed an average of 4.6 years (range: 0–17). During the follow-up period of 1.4–11.5 years, 23% of the patients reported increasing dysphagia and 36.7% reported stable symptoms. No change in endoscopic features was identified in 6 of the 7 patients in whom a subepithelial component could be analyzed, but an increase in fibrosis and thickening was documented.

Although a therapy with topical steroids had been described in children in 1998 [11], 2003 saw the therapies become established in adults by Arora et al. [12], and the use of montelukast medication was described by Attwood et al. [13] in the same year. These options now gave some direction to the therapy in addition to dilatation of strictures. Following these publications there was a rapid rise, almost logarithmically, with many hundreds of reports being published annually. From descriptions in the years 2003–2008 it became clear that there were a range of endoscopic phenotypes of EoE. Although not initially recognized, the patterns of linear furrows, circular ridges and more defined rings (trachealization), the presence of white microabscesses, and the complication of severe strictures in some were all manifestations of EoE [14, 15]. It is still not clear why EoE presents in these different phenotypes or whether they signify a different prognosis or disease pattern of responsiveness to therapy. During the years 2004–2006, 8 additional case series were described in multiple geographic locations (table 1) [16–23]. The total number of patients remained small, amounting to <300 reported patients, until after 2007 when case series with >300 patients began to appear. The central pathology laboratories in the USA are now aggregating information on >14,000 patients with this condition, indicating how frequently this disease is now recognized.

The development of international consensus guidelines has been a very important milestone in EoE, especially in the absence of good randomized controlled data on the therapy and outcome of care. The 2007 guideline of the American Gastroenterology Institute [24] was very helpful in defining the disease, and the update in 2011 [25] has provided detail on the value of investigations, the
current therapies, and the development of complications, particularly stricture and perforation. EoE is now the commonest cause of spontaneous perforation of the esophagus, although it is usually a partial perforation, and treated differently to the original complete disruption originally described by Boorhaeve. In 2008, 15 years after the first case series was published, the condition finally gained an ICD-9 classification: 530.13.

A key feature in managing patients with EoE is to understand that they are not suffering GERD. Low concentrations of esophageal eosinophils are commonly seen in GERD, but these usually only amount to 1–5/HPF. It is also not clear how common eosinophils are present in a normal population, but the study of Ronkainen et al. [26] (2007) in the Swedish town of Kalixanda is very revealing. They showed that in 1,000 randomly chosen subjects, 0.1% of the population had eosinophil concentrations of >20/HPF and 0.2% >15/HPF on biopsy 2 cm above the ZE line. Thus, EoE was extremely rare in a normal population, but the study of Ronkainen et al. [26] (2007) in the Swedish town of Kalixanda is very revealing. They showed that in 1,000 randomly chosen subjects, 0.1% of the population had eosinophil concentrations of >20/HPF and 0.2% >15/HPF on biopsy 2 cm above the ZE line. Thus, EoE was extremely rare in a normal population. In some clinical series of EoE, higher rates of reflux are documented [27–29], but these studies are confounded by the fact that the centers are reference centers for GERD and thus the referral population in those centers is not representative of the wider population. We looked at the frequency of EoE in a confirmed GERD population as part of a randomized controlled trial of medical and surgical therapy in the LOTUS trial [30, 31] and took biopsies when the patients were off medication for 7 days. Out of 541 patients, only 7 had concentrations of epithelial eosinophils >20/HPF, and an additional 3 had concentrations of epithelial eosinophils >15/HPF. The total incidence of EoE by simple counting of eosinophils in that reflux population was 1.8% – not dissimilar to the normal population of Kalixanda. According to Lee et al. [22], the diagnosis of EoE is more than just counting eosinophils, as it involves other biological changes such as increased extracellular major basic protein deposition in the esophageal mucosa of EoE, which is not seen at all in patients with GERD [32].

Hirano [33] recently reemphasized the need to perform biopsies while the patient is on proton pump inhibitors in order to refine the diagnosis and treatment of EoE to fit recent guidelines. While a subset of GERD patients may have high eosinophil counts and respond to proton pump inhibitors (the proton pump inhibitor-sensitive phenotype), these patients do not fit the diagnosis of EoE and present little therapeutic challenge.

Distinguishing EoE from GERD is very important in order to prevent years of ineffective treatment in nonrefluxing patients. The extreme cases are those subject to antireflux surgery for EoE; a number of case reports have shown this is more common in children. The original description of Kelly et al. [9] had 2 such patients, and our own report, Lamb et al. [34], was of a 12-year-old boy with a tight upper esophageal stricture who did not improve after Nissen fundoplication. Five years later, following accurate diagnosis, he responded fully to topical steroids and dilatation. Having not eaten anything solid for 10 years, he then enjoyed a completely normal diet. This severity of quality of life restriction by EoE is sometimes quite alarming, and the value of an accurate diagnosis and effective therapy is equally dramatic.

**Pathophysiology**

Over the past 10 years there have been huge strides in understanding the immunology and pathophysiology of EoE. This has raised expectations of effective immune-based treatments. Other papers in this volume focus on this area, which now has a huge wealth of information, and it is expected that this will provide avenues to research new drug treatments. The reasons why dysphagia occurs is clear in those with stricture, but not clear in some patients who just have linear furrows, or with microabscesses [35]. It is unlikely that the dysphagia is re-
lated to motility disorder, but more likely that it is due to stiffness in the submucosal, or perhaps muscular, layers of the esophageal wall. It is now feasible to measure the compliance of the esophageal wall using impedance planimetry (EndoFLIP) [36], and this may be a great help in identifying which patients would benefit from dilatation, and which levels of the esophagus require dilatation and by how much.

**Randomized Clinical Trials**

Despite huge strides in our knowledge, the development of new treatment strategies through randomized clinical trials has been relatively slow. The main therapy with proven benefit, topical steroids, has produced some confounding results. Placebo-controlled trials of budesonide have shown its effectiveness [37], and placebo-controlled trials of oral viscous budesonide in children [38] have been conclusive. However, these well-conducted studies reveal a difference between symptom benefit and clearance of histological abnormality: medium doses of steroids produce the most effective symptom benefit but do not clear epithelial infiltration with eosinophils, while the highest doses of topical budesonide can abolish intraepithelial eosinophils but not improve the overall symptom benefit. It is not understood why symptom improvement can occur without eosinophil clearance, and it remains to be worked out if this has a bearing on the development of long-term complications such as fibrosis and stricture.

The second major drug group in EoE therapy are the biological modifiers involved in the IL-5 and IL-13 pathway mediated by eotaxin 3 [39] and activating the T2 helper cell population. Studies of infliximab, mepolizumab, and CRTH2 antagonists have all shown insufficient clinical benefit for widespread use [40–42]. Initial studies on these antagonists have shown changes in the biological behavior of disease markers, but have not yet produced a generally applicable medical alternative to topical steroids. One of the difficulties in drug development has been the lack of a disease severity index and a poor prediction of the future likelihood of complicated EoE disease.

**Dilatation**

At the moment there are no published controlled trials of dilatation therapy to guide the clinician in precisely when and how to perform esophageal dilatation for patients with EoE [45, 46]. However, greater understanding of the role of dilatation and how it should be gauged is being developed.

**Conclusion**

EoE is now a well-established distinct disease about which much has been learned. It has become commonly diagnosed. EoE should be considered as one of the key differential diagnosis in any patient with a long-standing history of intermittent or continuous dysphagia. Since the description of this condition in case series in the early 1990s, the understanding of its pathobiology has increased and this continues with new understanding of its genetic profiling [47, 48]. A limited number of randomized clinical trials have been performed. More needs to be done. It is expected that we will need a disease severity index that includes endoscopy, pathology, and clinical symptoms. Developing both adult and childhood EoE quality of life scores will be an important step in guiding treatment practices, preventing complications [49], improving disease education, and standardizing research protocols.

**Disclosure Statement**

The authors declare that no financial or other conflict of interest exists in relation to the content of the article.
References


