Clinical Features of Eosinophilic Esophagitis

Stephan Miehlke

Center for Digestive Diseases, Internal Medicine Center Eppendorf, Hamburg, Germany

Key Words

Eosinophilic esophagitis · Dysphagia · Bolus obstruction · Endoscopy

Abstract

Eosinophilic esophagitis (EoE) may affect individuals at any age with a predominance for Caucasian males. The clinical manifestation of EoE is strongly age dependent. While dysphagia and food impaction are typical lead symptoms in adults and adolescents, infants often present with unspecific symptoms such as feeding problems, abdominal pain and vomiting. Some EoE patients may also experience heartburn. Therefore, EoE should always be considered in cases of heartburn refractory to antireflux therapy. Concomitant allergic diseases such as asthma, rhinitis and eczema are prevalent. Peripheral eosinophilia and elevated total serum IgE values are found in up to 50 and 70% of cases, respectively. Endoscopic features of EoE are variable and none of them is pathognomonic. Frequent findings are mucosal edema, furrows, exudates and corrugated rings. These endoscopic abnormalities have high specificities (90–95%), but low sensitivities (15–48%). A novel grading and classification system for the endoscopic assessment of EoE has been proposed which includes fixed rings, exudates, furrows and edema as major features. This classification system demonstrated good interobserver agreement among pediatric and adult

gastroenterologists, and presents a useful tool to standardize endoscopic assessments and to further investigate the relation between endoscopic manifestation, clinical activity and response to treatment in EoE. Long-term follow-up studies have shown that EoE is a chronic disease causing recurrent dysphagia in the majority of cases. The prevalence of strictures significantly increases with the duration of disease, which stresses the importance of early diagnosis and consequent treatment of EoE.

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Introduction

Eosinophilic esophagitis (EoE) is an increasingly recognized, chronic and antigen/immune-driven inflammatory disease of the esophagus [1]. Since the first description in the literature some 20 years ago, the number of studies on EoE has increased exponentially. Meanwhile, EoE has evolved into the second most common cause of chronic esophagitis after gastroesophageal reflux disease (GERD), and now represents the primary cause of dysphagia in young male patients. Finally, it is considered to be the most common of all eosinophilic gastrointestinal disorders.

EoE is predominantly found in westernized countries and geographical areas with higher socioeconomic devel-

Table 1. Similarities and differences in the clinical appearance of pediatric and adult EoE (adapted from [5])

	Adults	Children
Symptoms	dysphagia (solid food), food impaction, retrosternal pain	abdominal pain, chest pain, heartburn, coughing, decreased appetite, food refusal, anorexia, dysphagia, nausea, regurgitation, sleeping difficulties
Demographics	male Caucasians predominant	
Physical exam	normal	sometimes failure to thrive
Allergic predisposition	airborne allergens predominant	food allergens predominant
Concomitant allergic diseases	asthma, eczema, allergic rhinitis	
Lab values	peripheral eosinophilia 5–50%, total serum IgE ≈70%	

opment. However, the disease has been reported to affect individuals of every race, gender and age [2–4]. The current knowledge of the etiology and the underlying mechanisms of eosinophilic esophagitis is still limited. Although there appear to be distinct differences between eosinophilic esophagitis in pediatric patients and adults, it is generally accepted as the same disease entity [5, 6]

Symptom Presentation of EoE

EoE can affect individuals of any age and has in fact been described in patients ranging in age from 1 to 98 years [3]. Throughout the literature, EoE has been described as a predominantly male disorder both in children and adults, being at last three times more prevalent in males than in females [2–4]. The clinical presentation of EoE is strongly dependent on the patient's age and ability to communicate symptoms. In fact, more than any other aspect of the disease, the symptoms leading to endoscopy and diagnosis vary considerably between children and adults (table 1). In children suffering from EoE, the symptom pattern is rather unspecific, including dyspepsia, heartburn or abdominal pain as the most common symptoms [3]. However, pediatric patients may additionally complain about nausea, regurgitation, chest pain or sialorrhea. Finally, decreased appetite, food aversion, failure to thrive, sleep disturbances and respiratory complaints may be associated with pediatric EoE.

In contrast, adolescent and adult EoE patients usually present with dysphagia for solid foods and/or bolus impaction. In a study of 400 consecutive adult patients presenting for routine endoscopy, EoE was found in 6.5% of

the cases [7]. In this cohort, EoE was significantly associated with dysphagia, food impaction, male gender, age <50 years and asthma. Several series have reported dysphagia as the leading symptom in more than 70% of cases. However, food impaction has been the symptom that most often led to the diagnosis [3, 8–10]. Food impaction is often associated with acute severe retrosternal and chest pain that can potentially lead to immediate hospitalization and emergency endoscopy, which in turn is associated with a higher risk of complications. With increasing awareness for EoE in the future, it is likely that dysphagia itself will become the most prominent symptom leading to a rapid diagnosis of EoE in adults. Dysphagia may also be a quite early event in the development of EoE as suggested by a case of a 44-year-old woman who rapidly developed a full clinical picture of de novo EoE including severe dysphagia, confluent white exudates on endoscopy and severe eosinophilic inflammation of esophageal biopsies within the first 4 weeks of sublingual immunotherapy for hay fever [11].

In clinical practice it is important to realize that EoE patients often adapt long-term coping strategies to guarantee feeding and to avoid bothering symptoms. Adult EoE patients usually do not show any clinical signs of malnutrition at diagnosis or during the evolution of the disease. In the evaluation of patients with suspected EoE, it is therefore recommended to use more sophisticated questions in tools to identify the presence and the burden of dysphagia. Questions such as 'Do you wash food down with liquids?', 'Do you chew your food for a long time?', 'Do you avoid foods such as meat or breads?' or 'Are you usually the last one to leave the table?' may be helpful in this matter [5].

Fig. 1. Endoscopic manifestations in adult EoE patients enrolled in a European multicenter trial: white exudate (a), longitudinal furrows (b), diffuse edema (c), fixed rings (d), severe stricture (e), and rings, furrows and edema (f) [14].

Reflux symptoms are quite common in adult EoE patients; however, the prevalence rates differ among studies and range from 9 to 94% [4, 12, 13]. In a recent European multicenter study of 76 adult EoE patients [14], one third of the patients reported reflux symptoms and to a similar magnitude retrosternal pain or odynophagia in addition to the more prevalent and prominent dysphagia (fig. 1; table 2).

Natural Course of Disease

Little is known about the natural course and the long-term outcome of EoE. In analogy to other inflammatory bowel diseases, it can be assumed that EoE may be a progressive disease which, if untreated, may lead to irreversible long-term structural damage of the esophagus. However, the knowledge about progression of stricture formation in EoE is limited. In an early prospective study, 30 adult EoE patients were followed for a mean of 7 years without active medical therapy [15]. In this cohort, both dysphagia and esophageal eosinophilia persisted in the vast majority of patients while the overall severity of dysphagia and eosinophilia declined only marginally. A more recent retrospective study in 220 patients of the Swiss EoE database shed more light on the natural history of EoE by demonstrating a significant association between the diagnostic delay and the prevalence of esophageal strictures [16]. For example, the prevalence of esophageal strictures was 17% in patients who were diagnosed within 2 years of symptom onset and increased up to 71%

Table 2. Clinical presentation of adult EoE patients enrolled in a European multicenter trial [14]

Patients	76
Males, %	83
Mean age (range), years	39.7 (18–70)
Mean BMI (range)	24.8 (19.0–36.7)
Symptoms, %	
Dysphagia	100.0
Food impaction	65.8
Odynophagia	35.5
Retrosternal pain	38.3
Heartburn	32.9
Regurgitation	35.5
Abdominal pain	18.4
Diarrhea	7.8
Weight loss	2.6
Allergic comorbidities, %	64.5
Allergic rhinitis	50.0
Allergic conjunctivitis	19.7
Allergic asthma	19.8
Atopic eczema	9.2
Food allergies	21.1
Duration of dysphagia >1 year, %	50
Established disease, %	64
Previous steroids, %	
Fluticasone	22.4
Budesonide	3.9
Prednisolone	6.6
Previous dilatation, %	13

Fig. 2. Natural course of EoE: retrospective study in 200 adult EoE patients [16].

in patients with a diagnostic delay of more than 20 years (fig. 2). Diagnostic delay turned out to be the only risk factor for strictures at the time of EoE diagnosis. These data clearly indicate that it is of utmost importance to minimize the diagnostic delay in EoE in order to avoid potentially irreversible structural damage of the esophagus. So far, it seems that EoE itself is not associated with a decreased life expectancy or with an increased risk of developing malignant or premalignant lesions; however, more observational long-term studies are clearly required to confirm this.

Differential Diagnosis

Due to a potential symptom overlap, GERD represents the clinically most common and most relevant differential diagnosis to EoE [9, 17]. Gastroesophageal reflux may by itself cause esophageal eosinophilia, and patients with GERD may also suffer from dysphagia in addition to their reflux symptoms. On the other hand, EoE may lead to an impaired function of the lower esophageal sphincter, which in turn may promote increased gastroesophageal reflux [18, 19]. Finally, a subgroup of EoE patients does substantially respond to proton pump inhibitor (PPI) therapy, both clinically and histologically [20]. This observation had led to the term ‘PPI-responsive esophageal eosinophilia’ [1]. Therefore, the differentiation between EoE and GERD often remains a considerable challenge in clinical practice. This issue has been addressed in a retrospective study of 23 adult EoE and 20 adult GERD patients in which patient age, gender, weight loss, atopy, dysphagia, bolus impaction, PPI refractory heartburn, odynophagia, peripheral eosinophilia and serum IgE were subjected to

logistic regression analysis [21]. As a result, the optimal differentiation between EoE and GERD was possible by the equation blood eosinophilia + bolus impaction + PPI-refractory heartburn for EoE. If at least 2 of these factors were present, the sensitivity and specificity for the diagnosis of EoE was 91 and 100%, respectively.

Other differential diagnoses include eosinophilic gastroenteritis, hypereosinophilic syndromes, infectious or drug-induced esophagitis, autoimmune diseases and Crohn’s disease [1].

Allergy Testing in EoE

EoE is clearly associated with allergies in both children and adults [22]. Comparable to other published series, allergic comorbidities including allergic rhinitis, conjunctivitis, asthma and atopic eczema were found in 65% of adult patients participating in a European multicenter trial [14]. Peripheral eosinophilia and elevated serum IgE levels are usually found in 50 and 75% of patients, respectively [1]. Food-specific IgE or skin prick test results may be positive in over 80% of adult EoE patients [23]; however, elimination of foods that gave positive results failed to achieve disease remission, and response to a food elimination diet has been observed in patients who had negative allergy test results. Furthermore, in adult EoE patients who responded to a six-food elimination diet and relapsed after step-wise food reintroduction, a prick test was predictive for the responsible food allergen in only a minority of cases [13, 24]. These findings suggest dissociation between IgE-based food allergy test results and true EoE trigger foods. Therefore, allergy testing can be used to help identify food sensitizations associated with

Fig. 3. Diagnostic validity of endoscopic features of EoE – meta-analysis of 100 studies including 4,678 EoE patients [29]. PPV = Positive predictive value; NPV = negative predictive value.

EoE, but none of the currently available techniques has proven useful or reliable for the management of EoE in clinical practice.

Impact of EoE and Patient Quality of Life

Data on health-related quality of life (QoL) in EoE patients are still sparse. QoL assessment in pediatric EoE is particularly challenging because certain aspects often expressed by diseased children themselves may not be captured by standard questionnaires or because the patient's concerns may differ from the concerns reported by their parents. QoL was assessed in a case-control study of EoE patients in early adulthood more than 15 years after the histological diagnosis of EoE [25]. Three out of 4 patients had persistent dysphagia and food impaction as adults and expressed a significantly worse QoL than matched chronic esophagitis and healthy control subjects. Furthermore, EoE has a great impact on several psychological and social domain functions. Current research aims to develop and validate an adult eosinophilic esophagitis QoL questionnaire as a reliable disease-specific measure of health-related QoL based on 37 items with 5 subscales [26]. A recent study with 64 EoE patients showed that 69% of the patients experienced psychosocial problems including social difficulties (64%), anxiety (41%), sleep difficulties (33%), depression (28%) and school problems (26%). Adjustment problems were identified in 44% of the patients and were significantly more common in older than in younger patients [27]. Anxious behavior and depressive feelings increased with age. These findings indicate that psychosocial evaluation should be included in the management of EoE patients, especially in pediatrics and adolescents.

Table 3. Endoscopic classification and grading of EoE (modified from [30])

	Agreement experts/nonexperts, %	κ value experts/nonexperts
Major features		
<i>Fixed rings</i>		
Mild/moderate/severe	69/71	0.50/0.50
Also referred as concentric rings, corrugated esophagus, corrugated rings, ringed esophagus, trachealization		
<i>Exudates</i>		
Mild/severe	81/74	0.61/0.45
Also referred to as white spots, plaques		
<i>Furrows</i>		
Mild/severe	79/81	0.48/0.57
Also referred to as vertical lines, longitudinal furrows		
<i>Edema</i>		
Mild/severe	90/77	0.64/0.33
Also referred to as mucosal pallor, decreased vascular markings		
Minor features		
Crepe-paper esophagus	98/90	0.85/0.50
Stricture	82/78	0.56/0.49
Feline esophagus	66/67	0.10/0.12
Narrow-caliber esophagus	80/73	0.38/0.29

Endoscopic Manifestations of EoE

Upper endoscopy is the first and most important step in the diagnostic work-up of patients with dysphagia. A considerable number of endoscopic findings have been described in EoE; however, none of them can be regarded as specific or pathognomonic [1, 17, 28]. These features

can appear in random combination and represent evidence for active inflammation and/or fibrosis. A subset of EoE patients may even present with an endoscopically normal-looking esophagus. Therefore, clinicians need to maintain a high degree of suspicion and to always take multiple esophageal biopsies, even if the mucosa appears to be normal [1]. Endoscopic features such as mucosal edema, white exudates or longitudinal furrows are generally regarded as signs of active inflammation, while strictures, corrugated rings and stenoses indicate the presence of fibrosis and tissue remodeling. There are no systematic studies to compare endoscopic features of EoE between pediatric and adult patients. However, the general impression is that signs of active inflammation are more common in children while signs of fibrosis and remodeling are more frequently observed in adult patients, suggesting a progressive course of disease in a considerable number of patients [5, 6].

The validity of the endoscopic features of edema, exudates, furrows, strictures and rings were investigated in a meta-analysis including 100 studies with 4,678 EoE patients and 2,742 controls (fig. 3) [29]. While these signs showed an insufficient sensitivity (15–48%), the specificity was impressively high (90–95%). As a result, the positive and negative predictive values ranged from 51 to 73% and from 74 to 84%, respectively. The meta-analysis fur-

ther showed that at least one endoscopic sign was found in 83% of the patients, while endoscopy was considered normal in 17% of patients. Interestingly, the percentage of normal endoscopies was significantly lower in prospective compared to retrospective studies (7 vs. 20%), suggesting an increasing awareness of the endoscopist to look for subtle changes in the esophageal mucosa.

With the aim to further improve and standardize the endoscopic diagnosis of EoE, a novel endoscopic classification and grading system has been proposed as a result of a validation study of endoscopic videos from 25 EoE patients, which were reviewed by 21 adult and pediatric gastroenterologists with various experience levels [30]. The proposed system defines a common nomenclature of and severity scores for the assessment of EoE activity and has shown good interobserver agreement for the major endoscopic EoE features of rings, exudate, furrows and edema (table 3). This classification and grading system will certainly be useful for future clinical trials and will facilitate standardization and comparison of endoscopic findings in clinical practice.

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