Eosinophilic esophagitis and esophageal motility changes

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Abstract

Eosinophilic esophagitis is a chronic condition that can affect any age, with an increasing prevalence in the last years. Esophageal symptoms are accompanied by normal endoscopic findings or changes suggestive for the disease, like rings, furrows, exudates, or strictures. The definitive diagnosis is based on esophageal biopsies, with identification of at least 15 eosinophils/high power field. In about 1/3 of patients esophageal motility abnormalities are observed. Ineffective esophageal motility is the most frequent. In some cases, major motility disorders, such as achalasia can be observed. The treatment depends on the patients' preferences and on symptoms severity, and usually a step-up approach is used. A diet change can be helpful in more than half of patients, some respond to proton pump inhibitors. In non-responders, short courses of topical corticosteroids are recommended. Endoscopic procedures might be helpful in patients with obstructive motility changes, non-responding to medical therapy. This review discusses the motility changes observed in patients with eosinophilic esophagitis.

Keywords: eosinophilic esophagitis, endoscopy, manometry

Introduction

Eosinophilic esophagitis is an immune-mediated disease characterized by eosinophilic infiltration of the esophagus. The consequences are both macroscopic and functional. During upper gastrointestinal endoscopy, white exudates, rings, longitudinal furrows or even stenosis can be observed [1]. The disturbed esophageal function is responsible for symptoms like dysphagia or food impaction, but also for motility changes observed during esophageal manometry, such as ineffective esophageal motility. Esophageal biopsies are mandatory for diagnosis, 15 eosinophils/high power field (HPF) confirming the disease. The disorder can be observed at any age but is more often between 30 and 40 years of age. It is three times more common in males than in females, and the common symptoms are dysphagia, food impaction and reflux symptoms [1]. This inflammatory condition can slowly progress in time to fibrosis and reduced esophageal caliber [2]. Therefore, correct management is of utmost importance, with diet, proton pump inhibitor (PPIs) and topical steroids as the current therapeutic options for these patients. There is an increase in incidence and prevalence of eosinophilic esophagitis (EoE) in the last years, world-wide, with incidence around 7 new cases per 100,000 inhabitants/year, and a prevalence between 13-49 cases per 100,000 inhabitants [1]. This short narrative review covers the functional changes observed during manometry in patients with EoE.

Pathophysiology of eosinophilic esophagitis

The pathogenesis of EoE is not completely understood. Environmental factors such as antibiotic use or excessive hygiene in childhood seem to play a role [3]. Recent studies showed that there also is genetic susceptibility, the polymorphism of CAPN14 gene leading to impaired epithelial barrier function [4]. Other susceptible genes induce a Th2-type immune response, and were observed in other allergic diseases [5]. The widespread use of PPIs in the last years, seem also to

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play a pathogenetic role in EoE development, by interfering with the peptic digestion of food allergens [6]. Thus, an altered epithelial barrier function allows antigens (from food or microbiota) to penetrate underneath the epithelium and induce a Th2 immune response. Local cytokines release determines the accumulation of eosinophils, and their products alter more the epithelial barrier, stimulate fibrosis, and damage the neurons, leading to altered motor and sensory esophageal function [7].

Clinical manifestations and diagnosis of eosinophilic esophagitis

The symptoms of EoE vary with age. In small children and during childhood food refusal, gagging, inadequate growth, vomiting and gastroesophageal reflux disease (GERD) symptoms were reported [8]. Dysphagia, food impaction and heartburn are the most common symptoms in older children and in adults [9]. In a recent study on 109 EoE patients, obstructive symptoms were very common (dysphagia in 90% of cases and bolus impaction in 67%), while GERD symptoms were reported by only 40% of patients [10]. Regarding food impaction, studies showed that EoE is the commonest cause, being observed in 70% of cases [11].

The diagnosis of EoE imposes an upper gastrointestinal (GI) endoscopy with esophageal biopsies. During endoscopy, fibrotic (rings, narrowing) or inflammatory changes (oedema, exsudates, furrows) can be observed. Among endoscopic findings, linear vertical furrows, esophageal concentric rings, and oedema (with pallor or decreased vascularization) are the most characteristic changes. In some cases, white spots, or plaques (exudates), strictures or mucosal fragility (crepe-paper esophagus) are observed [12]. Esophageal mucosa can be macroscopically normal, therefore at least 6 biopsies (3 from the proximal esophagus, and 3 from the distal esophagus) are required to diagnose EoE [1].

Esophageal manometry in eosinophilic esophagitis

According to current guidelines, esophageal manometry is not mandatory in patients with EoE. However, when performed, manometry is abnormal in 30-40% of the patients [13]. One of the studies using prolonged esophageal manometry reported a good correlation between abnormal motor function (i.e. high-amplitude contractions or ineffective peristalsis) and dysphagia [14]. However, eosinophil count and dysphagia scores seem to be similar in patients with normal esophageal motility compared to those with abnormal esophageal motility [15]. The longer the disease duration, the higher the probability of abnormal motor function [16]. There are data that after treatment with budesonide, abnormal esophageal motility resolves in the majority of cases [17].

A recent study on 109 patients with EoE reported esophageal motor disorders in 38% of patients. Among esophageal motor disorders, 17 patients had major motor disorders (achalasia or obstructive motor disorder). It is worth noting that 50% of these patients did not respond to the specific treatment of EoE and required pneumatic dilation or myotomy. In some cases, after dilation, there was a positive response to topical steroids, suggesting that a normal bolus transit is important for symptom response to EoE therapy [10]. This study underlined the importance of motility studies in patients with EoE, especially if symptoms persisted despite adequate medical treatment. In these patients, the presence of a major esophageal motility disorder should be identified, because the endoscopic treatment can lead to symptoms' resolution.

Ineffective esophageal motility and early pan-esophageal pressurization were the changes most frequently reported in motility studies [10,13-18]. It is worth mentioning that 1 in 7 patients with EoE might have an underlying obstructive motor process, as shown by Ghisa et al [10]. Table I summarizes the main findings of the motility studies performed in patients with EoE.

Among the parameters of HREM, the measure of the intrabolus pressure (IBP) could be used to differentiate between fibro-stenotic and inflammatory patterns in patients with EoE, as showed by Colizzo et al [20]. In their study, IBP was had significantly higher in patients with fibro-stenotic disease compared to patients with inflammatory pattern. These changes of IBP were reported in previous studies [13,17,19] (see Table I), and are likely related with the change of esophageal luminal diameter. The smaller the diameter, the higher the pressure required to distend the esophageal wall.

Treatment of eosinophilic esophagitis

Currently there are three main therapeutic options for patients with EoE. A step-up approach is used in patients with mild symptoms. An empiric elimination diet (2-, 4- or 6-food elimination diet) can be tried first if the patient is willing and compliant. The foods to be avoided are milk protein and wheat first, soy, eggs, peanuts/tree nuts, and seafood afterwards. In non-responders, PPIs in double dose for 8 weeks is recommended. Response to treatment should be both clinical and histological. In case of failure, or in patients presenting with severe symptoms, topical corticosteroids, like budesonide and fluticasone for 8 weeks are used. If symptoms persist, endoscopy should be repeated [21]. Based on current knowledge, when dysphagia persists despite treatment, esophageal motor function should be assessed, and if present, major motility disorders should be addressed using endoscopic or surgical procedures [10].

Table I. Esophageal manometry studies in patients with eosinophilic esophagitis.

Study	Patients	Manometry technique; proportion of abnormal esophageal motility in EoE patients	Main results
Remedios et al. 2006 [18]	23 EoE patients	Conventional manometry	- Only one patient had aperistalsis
Roman et al. 2010 [13]	48 EoE pts, 48 GERD pts and 50 controls	HREM 37%	- The most frequent abnormalities: weak peristalsis and frequent failed peristalsis - Pan-esophageal pressurization- 17% of EoE vs. 2% of GERD pts - compartmentalized pressurization was present in 19% of EoE and 10% of GERD patients - prevalence and type of motility disorders were similar with GERD in
Moawad et al. 2011 [15]	75 EoE pts	Conventional manometry 37%	- 33.3% pts had IEM, and 3.6% had nutcracker esophagus - Eosinophilic count was not different between groups (normal, or mild, moderate, or severe IEM), nor dysphagia scores
Martin Martin. et al. 2011 [19]	21 EoE pts, 21 controls	HREM	- The most frequent abnormalities in EoE: pan-esophageal pressurization (48%) and peristaltic dysfunction (failed peristalsis or small breaks)
Van Rijn et al. 2014 [16]	31 EoE pts, 31 GERD pts and 31 controls	HREM	- Weak and failed peristaltic integrity were observed in 12%, and 27% of EoE patients respectively, more often compared to controls, but similar when compared to GERD patients - Patients with normal motility had similar symptoms and signs compared to patients with motility changes - Patients with abnormal motility had a longer duration of symptoms
Nennstiel et al. 2016 [17]	20 EoE pts	HREM 35%	- The most frequent abnormalities: early pan-esophageal pressurizations and weak peristalsis - 8 weeks after treatment with Budesonide, esophageal motility was restored to normal in 86% of cases - The decrease of intrabolus pressure remained was not significant
Ghisa et al. 2020 [10]	109 EoE pts	HREM 38%	- 22% pts had IEM and frequent failed peristalsis - 7.3% pts had achalasia - 7.3% pts had other obstructive motor disorder: distal esophageal spasm, jackhammer esophagus, and esophagogastric junction outflow obstruction

EoE, eosinophilic esophagitis; GERD, gastroesophageal reflux disease; HREM, high resolution esophageal manometry; Pts, patients; vs., versus; IEM, ineffective esophageal motility

Conclusion

EoE is a persistent inflammatory condition which untreated can determine esophageal stenosis. In every patient with dysphagia and food impaction, endoscopy should be performed with caution, to identify slight esophageal changes, and esophageal biopsies are mandatory. In selected patients with persistent symptoms despite specific treatment, esophageal manometry should be performed to identify major motility disorders that require interventional treatment.

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