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Title: Diagnostic approach to eosinophilic oesophagitis: pearls and pitfalls

Alain Schoepfer, MD

Correspondence address:

Alain Schoepfer, MD, PD+MER1

Division of Gastroenterology and Hepatology

Centre Hospitalier Universitaire Vaudois / CHUV

Rue de Bugnon 44, 07/2409

1011 Lausanne, Switzerland

Tel: + 41 21 314 2394

Fax: + 41 21 314 4718

E-mail: alain.schoepfer@chuv.ch

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ABSTRACT

Eosinophilic oesophagitis (EoE) has first been described a little over 20 years ago. EoE has been defined by a panel of international experts as a “chronic, immune/antigen-mediated, oesophageal disease, characterized clinically by symptoms related to oesophageal dysfunction and histologically by eosinophil-predominant inflammation”. A value of ≥ 15 eosinophils has been defined as histologic diagnostic cutoff. Other conditions associated with oesophageal eosinophilia, such as gastro-oesophageal reflux disease (GERD), PPI-responsive oesophageal eosinophilia, or Crohn’s disease should be excluded before EoE can be diagnosed. This review highlights the latest insights regarding the diagnosis and differential diagnosis of EoE.

94 words (max 150)

Key words: Eosinophilic oesophagitis, PPI-responsive oesophageal eosinophilia, eosinophils

INTRODUCTION

Eosinophilic oesophagitis (EoE) has first been described as distinct disease entity in the early 1990s.[1,2] The first comprehensive definition of EoE was published in 2007.[3] Hence, until 2007, the diagnosis of EoE was not standardized. In the updated 2011 guidelines, EoE was defined by an international expert panel as “a chronic, immune/antigen-mediated, oesophageal disease, characterized clinically by symptoms related to oesophageal dysfunction and histologically by eosinophil-predominant inflammation”.[4] This diagnostic definition highlights that there is no single test to affirmatively diagnose EoE, but that the diagnosis relies rather on a combination of typical symptoms and characteristic histologic findings (**Figure 1**). Of note, several differential diagnoses associated with oesophageal eosinophilia have to be excluded before EoE diagnosis can be established (**Table 1**).

NORMAL VALUES OF EOSINOPHILS IN THE GASTROINTESTINAL TRACT

Under normal conditions, the oesophageal epithelium is devoid of eosinophils. As such, every accumulation of eosinophils in the oesophageal mucosa can be described as oesophageal eosinophilia. However, eosinophils can be found in other segments of the gastrointestinal tract under normal conditions. A significant increase in the number of eosinophils from the oesophagus to the right colon can be observed (mean $\pm$ SD/mm²: 0.07 $\pm$ 0.43 for the oesophagus, 12.18 $\pm$ 11.39 for the stomach, and 36.59 $\pm$ 15.50 for the right colon), compared with a decrease in the left colon (8.53 $\pm$ 7.83).[5] Of note, eosinophil values in the different segments of the gastrointestinal tract were not different when Japanese were compared to Japanese Americans and Caucasians.[5] Knowledge of these normal values is important to judge if a patient has isolated EoE or oesophageal eosinophilia accompanied by an eosinophilic gastro-enteritis.

DEFINITION OF EOSINOPHILIC OESOPHAGITIS

The first diagnostic criteria for EoE were published by a consensus committee in 2007, followed by a revision in 2011.[3,4] The most recent guideline on EoE diagnosis and management was published in 2013 and proposed the following diagnostic criteria:[6]

- Symptoms related to oesophageal dysfunction
- Eosinophil-predominant inflammation in oesophageal biopsies with a peak eosinophil value of ≥ 15 eosinophils per high power field (magnification 400x)
- Mucosal eosinophilia is isolated to the oesophagus and persists after two months of treatment with a proton pump inhibitor (PPI)
- Secondary causes of oesophageal eosinophilia have been excluded
- A clinical and histologic response to treatment with swallowed topical steroids or diet elimination supports the EoE diagnosis but is not required

Typically, patients undergo first oesophageal biopsy sampling either related to endoscopic workup of dysphagia, thoracic pain, or a food bolus impaction. Most patients with these key symptoms will not be under therapy with PPI. Patients with documented oesophageal eosinophilia should then undergo an 8-week PPI treatment with single-or double standard dose. The duration of 8 weeks has been recommended in the diagnostic guidelines based on the fact that erosive or ulcerative reflux oesophagitis can take up to 8 weeks for endoscopic healing.[3,4,6] Patients should then undergo again oesophageal biopsy sampling when still being under PPI-therapy (**Figure 2**). [3,4,6] In case of EoE, oesophageal eosinophilia and symptoms of oesophageal dysfunction will persist. In case of GERD, reflux-associated symptoms and oesophageal eosinophils will disappear. In case of a PPI-REE, symptoms of oesophageal dysfunction as well as oesophageal eosinophils will

improve. However, as of yet, there exists no definition on how much the eosinophils and on how much symptoms have to improve. As EoE-related symptoms are not specific, there might exist a considerable delay between first symptom presentation and EoE diagnosis. In a retrospective study on 200 symptomatic EoE patients a median diagnostic delay of 6 years (interquartile range 2-12 years) was found.[7] Increasing duration of diagnostic delay increased the risk for structuring disease phenotype.

Of note, the diagnostic cutoff of ≥ 15 eosinophils/hpf has not been extensively validated. The currently established cutoff definition does not take into account the size of a high power field which has considerable variability. Peak eosinophil counts reported in various studies may not be necessarily comparable as different microscope types with different high power field sizes are used in different studies.[8] Reporting the observed peak eosinophil counts standardized to mm^2 could standardize this measure.

In addition, the precise PPI dose that should be used to establish the diagnosis is also uncertain. In children, age-appropriate dosing regimens with 1mg/kg body weight and in adults twice daily dosings have been suggested. However, twice daily standard dosages may not be covered by all health insurances and dosing equivalence between the various PPIs have not been clearly established. As such, a practical recommendation is to use PPI in standard doses equivalent for treatment of GERD.

CLINICAL DIAGNOSIS OF EOSINOPHILIC OESOPHAGITIS

The clinical manifestation of EoE is highly dependent on the age. Common symptoms in adults include dysphagia, food impaction, chest pain that is centrally located and does not respond to acid-suppressive therapy, GERD-like symptoms, or

upper abdominal pain.[9-16] Particular attention should be paid to assessment of behavioral modification strategies in the patient interview.[17] EoE patients should be systematically asked if they avoid certain food consistencies (such as red meat, chicken, bread, or dry rice), if they modify the food (e.g. cut it in tiny pieces or put it into a blender, or drink a lot to wash down the food).[17] In addition, patients should also be questioned how much time they need to ingest a regular meal. Patients with extreme EoE phenotypes such as a narrow-caliper oesophagus may ingest only liquid food and no longer participate in social activities such as eating out with friends, which may lead to social isolation and reduced quality of life.[18,19] A recently published case series has reported on adult EoE patients presenting with exercise-induced chest pain.[20] As such, underlying EoE should be considered in case of negative cardiologic workup of thoracic pain. Furthermore, patients presenting with a Boerhaave syndrome (spontaneous oesophageal perforation), oesophageal perforation following endoscopy, and deep mucosal tears associated with an endoscopy should be evaluated for underlying EoE.[21]

The symptom presentation in children varies depending on their age.[22-24] The following age-dependent leading symptoms were described: feeding dysfunction (median age 2.0 years), vomiting (median age 8.1 years), abdominal pain (median age 12.0 years), dysphagia (median age 13.4 years), and food impaction (median age 16.8 years).[25] A recently published study reported on pediatric EoE patients with an average follow-up duration of 15 years and described an increased rate of dysphagia (49 versus 6 percent) and food impaction (40 versus 3 percent).[26] These findings imply a disease progression over time and are consistent with data on EoE's natural history in an adult population.[7] There is increasing data that ongoing eosinophil-predominant inflammation results in development of oesophageal remodeling and fibrosis.[7,9,10,27,28] It is well documented that these underlying

changes are associated with EoE-associated endoscopic findings, such as stricture(s) and luminal narrowing which represent the main risk factor for food impactions.[7] According to our current knowledge, EoE symptoms are related to acute inflammatory changes that alter oesophageal motility or chronic inflammatory changes with reduced oesophageal compliance and luminal narrowings or a combination of both factors.[26-29]

HISTOLOGIC DIAGNOSIS OF EOSINOPHILIC OESOPHAGITIS

The main finding in EoE histology is oesophageal eosinophilia. **Figure 3** provides a representative example of an oesophageal biopsy sample with marked eosinophilia.

EoE patients typically have at least 15 eosinophils per high power field (hpf, 400x magnification) in at least one biopsy specimen after an 8-week treatment with proton pump inhibitors (PPI). This acid suppression is important as a proportion of patients will achieve complete histologic resolution under PPI treatment.[30,31]

Of note, the detection of oesophageal eosinophilia in the absence of symptoms related to oesophageal dysfunction is not sufficient to affirmatively diagnose EoE. During endoscopy, biopsies from the distal oesophagus as well as biopsies from the mid or proximal oesophagus should be taken.[32] The diagnostic accuracy of biopsies to diagnose EoE depends on their number. The sensitivity to diagnose EoE was 100% with 5 biopsies compared to a sensitivity of 55% when only one biopsy was taken.[33] A study by gastrointestinal pathologists evaluated the optimal number of biopsy fragments to establish a morphologic diagnosis of EoE in a consecutive series of 102 EoE patients.[34] The probability of one, four, five, and six biopsy fragments to contain >15 eosinophils/hpf was 63%, 98%, 99%, and >99%, respectively. Based on these findings, current guidelines recommend to take two to

four biopsies from the distal oesophagus as well as another two to four from the mid or proximal oesophagus.[6] Biopsies should be fixed in formalin or paraformaldehyde. The following other histologic findings that are suggestive of EoE have been reported: eosinophilic microabscesses, basal cell hyperplasia, papillary lengthening, superficial layering of eosinophils, extracellular eosinophil granules, and increased numbers of mast cells, B-cells, and Ig-bearing cells.[35-37] In addition to oesophageal biopsy specimens, biopsies should also be taken from stomach and duodenum to evaluate if there if they show an increased eosinophil count that would be compatible with eosinophilic gastroenteritis. The diagnosis of the latter would have an impact on treatment decisions.[6]

ENDOSCOPIC DIAGNOSIS OF EOSINOPHILIC OESOPHAGITIS

Several morphologic oesophageal features have been described in EoE patients.[10,13,16,23-25,33] Hirano and coworkers recently published an endoscopic grading system that takes into account white exudates (representing eosinophil microabscesses), rings, edema, furrows, and strictures.[38] However, the current clinico-pathologic definition of EoE points to the fact that endoscopic appearance alone is of limited utility in EoE diagnosis. An endoscopically normal esophagus may be found in up to 30% of EoE patients. A large meta-analysis compared 4678 EoE patients with 2742 controls and found the following frequencies of endoscopic findings in EoE patients: circular rings in 44 percent, strictures in 21 percent, edema in 41 percent, furrows in 48 percent, white exudates in 27 percent, and a small caliber oesophagus in 9 percent.[39] The sensitivity of individual endoscopic features suggestive of EoE was low a range from 15 to 48 percent and a high specificity ranging from 90 to 95 percent. As such, histology remains an important key element in EoE diagnosis irrespective of endoscopic appearance.

OTHER DIAGNOSTIC MODALITIES

Several other modalities have been described to diagnose EoE. However, these are not incorporated into the current EoE definition. The following chapter will describe these diagnostic modalities.

Association with allergies: there is a strong association of EoE with food allergies, environmental allergies, asthma, and atopic dermatitis. Estimations show that 28 to 86 percent of adult EoE patients and 42 to 93 percent of pediatric EoE patients have another allergic disease.[11,23,25,40-43] As such, every EoE patient should undergo evaluation by an allergist or immunologist. A major interest in the allergy workup is to identify food allergens that could be avoided in an elimination diet.[44]

Laboratory tests: As of yet, no serum markers have been identified to diagnose EoE. About 50 to 60% of EoE patients have elevated serum IgE levels.[45] Peripheral eosinophilia is found in 40 to 50 percent of EoE patients and may decrease under therapy with swallowed topical steroids.[46]

Genetic tests: Rothenberg et al. developed an EoE diagnostic panel, comprising a 96-gene quantitative polymerase chain reaction array and an associated dual-algorithm that uses cluster analysis and dimensionality reduction.[47] The diagnostic panel identified adult and pediatric EoE patients with approximately 96% sensitivity and 98% specificity when compared to the current “gold-standard” assessment using symptoms of oesophageal dysfunction and oesophageal eosinophilia. This diagnostic panel is not commercially available.

Endoscopic ultrasound: Endoscopic ultrasound in EoE patients revealed thickened wall layers.[48] Endoscopic ultrasound is difficult to standardize (e.g. volume of the water in the balloon) and relatively contra-indicated in patients with stricturing disease.

Oesophageal manometry: findings in oesophageal manometry of EoE patients are non-specific, and as such, routine manometry is not recommended.[49] **However, manometry is indicated if achalasia is suspected.**

Oesophageal string test and cytosponge: In order to avoid repetitive endoscopies in EoE patients, several groups have evaluated minimally invasive biologic measures, such as the oesophageal string test and the cytosponge, in order to assess the degree of histologic inflammation. Furuta *et al.* have recently published a study on the oesophageal string test, a minimally invasive tool to assess mucosal inflammation.[50] The authors demonstrated that the level of luminal eosinophil-derived proteins extracted from the oesophageal string correlated with the oesophageal peak eosinophil counts. As such, this test can be considered as a good measure of mucosal inflammation in children with EoE. The oesophageal string test will likely be useful in pediatric EoE patients needing repeated assessment of mucosal inflammation to spare these children the burden of repeated endoscopy under general anaesthesia.

Katzka *et al.* compared the accuracy, safety, and tolerability of oesophageal sample collection via Cytosponge, an ingestible gelatin capsule containing compressed mesh attached to a string, with those of oesophageal biopsies.[51] Oesophageal tissue samples were collected from 20 EoE patients using both Cytosponge and oesophageal biopsy sampling during endoscopy. Number of eosinophils per high-power field and levels of eosinophil-derived neurotoxin were determined; hematoxylin & eosin staining was performed. All 20 samples collected by Cytosponge were adequate for analysis. By using a cutoff value of 15 eosinophils per high power field, analysis of samples collected by Cytosponge identified 11 of the 13 individuals with active EoE (83%); additional features, such as abscesses were also identified.

Numbers of eosinophils in samples collected by Cytosponge correlated with those in oesophageal biopsies ($r = 0.50$, $P = 0.025$). Analysis of tissues collected by Cytosponge identified 4 of the 7 patients without active EoE (57% specificity), as well as 3 cases of active EoE not identified by analysis biopsy samples. Including information on the level of eosinophil-derived neurotoxin did not increase the diagnostic accuracy. All patients preferred to swallow Cytosponge, when compared to undergoing endoscopy. The authors concluded that the Cytosponge is a safe and well-tolerated method for collecting near mucosal specimens. Both minimally-invasive measures need further validation studies. The string test as well as the Cytosponge assess eosinophil-derived inflammation, but do not provide information regarding the fibrotic changes and the oesophageal caliper.

Measuring oesophageal compliance and diameter using endolumenal functional lumen imaging probe: Uncontrolled eosinophil-predominant oesophageal inflammation that persists over time leads to remodeling with formation of strictures.⁷ These structural oesophageal abnormalities may be detected by the means of endolumenal functional lumen imaging probe that helps physicians to monitor oesophageal wall distensibility both to assist in diagnosis of EoE and to track the progress of patients on various treatments.[52]

DIFFERENTIAL DIAGNOSIS

Oesophageal eosinophilia is not specific for EoE and thus the differential diagnosis includes a variety of conditions that can cause endoscopic and/or histologic alterations that look similar to EoE (**Table 1**).

PPI-REE describes patients with clinical and histologic features of EoE but who respond histologically and clinically to a PPI therapy.[53,54] The pathogenesis of

these patients remains poorly understood.[6,53] It is currently unknown if PPI-REE and EoE are distinct diseases.[53] PPIs block STAT6, which is involved in binding the eotaxin-3 promoter in oesophageal epithelial cells which might explain the anti-eosinophil effect in some patients.[55] Based on patient history, endoscopic and histologic findings, patients with PPI-REE cannot be discriminated from EoE patients.[56] After an initial response to PPI, patients might develop symptoms and eosinophilia consistent with EoE.[57] Of note, there exists currently no consensus on how to define “clinical” and “histologic” response to PPI therapy.

GERD is the most common differential diagnosis in patients with oesophageal eosinophilia. The peak number of ≥ 15 eosinophils/hpf does not discriminate GERD from EoE as peak eosinophils >100 /hpf can be observed also in GERD patients. Given the association of GERD with oesophageal eosinophilia, biopsies for EoE diagnosis should be taken after an 8 week PPI treatment or after an oesophageal pH-metric study has excluded reflux disease.[6] Several clinical, endoscopic, and histologic features were identified that might help in discriminating EoE patients from GERD patients. When compared to GERD patients, EoE patients are more often male, younger than 45 years, have concomitant allergies, present more often with dysphagia, oesophageal alterations such as rings, furrows, exudates, and are less likely to have a hiatal herniation or suffer from heartburn.[13] On the histologic level, large numbers of eosinophils, eosinophil abscesses, subepithelial lamina propria fibrosis, severe basal cell hyperplasia, eosinophil degranulation, and activated mucosal mast cells are more common in EoE patients when compared to GERD patients.[58]

SUMMARY

Eosinophilic oesophagitis is a clinico-pathologic disease diagnosed by the clinician based on symptoms of oesophageal dysfunction and an eosinophil-predominant inflammation with ≥ 15 peak eosinophils/high power field that persists despite an 8-week therapy with proton pump inhibitors (PPI). The eosinophil-predominant inflammation is restricted to the esophagus. Distinct endoscopic alterations such as white exudates, furrows, rings, edema, and strictures characterize patients with EoE. However, as the sensitivity of these distinct endoscopic features to diagnose EoE is low, they are not incorporated into the current EoE definition. Gastro-esophageal reflux disease (GERD) and PPI-responsive oesophageal eosinophilia (PPI-REE) represent the main differential diagnoses for oesophageal eosinophilia. Of note, it is impossible to discriminate patients with PPI-REE from EoE patients based on clinical, endoscopic, or histologic characteristics. PPI-REE is diagnosed if patients show a clinical and histologic response under PPI. As of yet, there exists no accepted definition regarding the extent of such a clinical and histologic response. Several rarer differential diagnoses such as esophageal Crohn's disease or achalasia must be excluded before EoE can be affirmatively diagnosed.

The pathogenesis and natural history of PPI-REE needs to be further defined and definitions regarding symptomatic and histologic response of PPI-REE patients under PPI need to be established. The development and validation of distinct instruments to capture symptom severity, endoscopic, and histologic activity, is the prerequisite for better understanding the relationship between symptom severity, endoscopic and histologic findings in patients with EoE and PPI-REE.

PRACTICE POINTS

- Eosinophilic oesophagitis (EoE) is a clinico-pathologic disorder characterized by symptoms of oesophageal dysfunction and eosinophil-predominant inflammation with a peak value of ≥ 15 eos/hpf after an 8-week PPI therapy
- Secondary causes of oesophageal eosinophilia need to be excluded
- A response to treatment (swallowed topical corticosteroids or elimination diets) supports, but is not required for EoE diagnosis
- Proton-pump inhibitor-responsive esophageal eosinophilia (PPI-REE) is diagnosed in case of symptomatic and histologic response under PPI.
- A clinical, endoscopic, and/or histologic response to PPI does not necessarily mean that gastro-esophageal reflux disease (GERD) is the underlying cause of the oesophageal eosinophilia.

RESEARCH AGENDA

- The pathogenesis and natural history of PPI-REE needs to further defined
- Definitions regarding symptomatic and histologic response of PPI-REE patients under PPI need to be established.
- The relationship between symptom severity, endoscopic and histologic findings in patients with EoE and PPI-REE need to be further evaluated.

TABLES

Table 1: Differential diagnosis of oesophageal eosinophilia.

Diseases associated with oesophageal eosinophilia
<p>Eosinophilic oesophagitis</p> <p>GERD</p> <p>PPI-responsive oesophageal eosinophilia</p> <p>Eosinophilic gastrointestinal diseases</p> <p>Oesophageal infections (e.g. fungal, viral, parasitic)</p> <p>Crohn's disease</p> <p>Celiac disease</p> <p>Achalasia</p> <p>Hypereosinophilic syndrome</p> <p>Pemphigus</p> <p>Vasculitis</p> <p>Connective tissue diseases</p> <p>Drug hypersensitivity</p> <p>Graft versus host disease</p>

FIGURES

Figure 1: The diagnosis of EoE is based on a combination of typical symptoms and marked oesophageal eosinophilia (marked in dark grey).

Figure 2: diagnostic approach for EoE and its most relevant differential diagnoses. Abbreviations: GERD, gastro-oesophageal reflux disease; PPI-REE, proton-pump inhibitor-responsive oesophageal eosinophilia.

Figure 3: eosinophilia in the oesophageal epithelium of an EoE patient (courtesy of Dr. Christian Bussmann, Institute of Pathology Viollier, Basel, Switzerland).

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*denotes particularly important reference

Figure1

Figure2

Figure3