

Clinical Evaluation of the Adult who has Eosinophilic Esophagitis

Alex Straumann, MD

KEYWORDS

- Eosinophilic esophagitis • Physical examination
- Laboratory abnormalities • Endoscopic signs
- Histologic findings

Eosinophilic esophagitis (EoE) may affect individuals at any age, and similar genotypic abnormalities are found in children and in adults, thereby indicating that the disorder is one single entity. However, some phenotypic manifestations of EoE are highly age dependent and justify a different management. The clinical evaluation of adult patients who have EoE entails the exceptional feature that treating physicians typically encounter apparently healthy individuals.¹ EoE cannot be described as an overt disease, nor is it, except for episodic complications, spectacular or dramatic. This characteristic is firstly due to the anatomic location of the esophagus, hidden deep within the chest cavity and, secondly, because in adults, EoE rarely evokes systemic effects, such as fatigue, fever, wasting, or severe pain. This presentation contrasts sharply with pediatric EoE, whereby general symptoms, such as food refusal, failure to thrive, and pain, alert family members and physicians early during the course of the disease.^{2,3} This unimpressive adult presentation may explain the fact that after symptoms commence in the adult, some 4 to 5 years usually pass before EoE is finally diagnosed.⁴ Nevertheless, gastroenterologists are familiar with this pattern of clinical appearance from other chronic gastrointestinal inflammatory diseases (eg, Crohn's disease or microscopic colitis). Despite the absence of a dramatic appearance, EoE is a relevant burden for most affected individuals, substantially impairing the patient's quality of life⁵ and associated with several relevant risks.⁶⁻⁹

In summary, the clinical evaluation of an adult patient who has suspected EoE requires a deep probing into the issue, firstly, by taking a thorough medical and family history and secondly, by using invasive examinations, even beyond the frontiers of the endoscope, using histologic and immunohistologic methods.

Department of Gastroenterology, Kantonsspital Olten, Roemerstrasse 7, CH-4600 Olten, Switzerland

E-mail address: alex.straumann@hin.ch

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DEFINITION

EoE is defined in adults, adolescents, and children as a clinicopathologic disease characterized by upper intestinal symptoms and dense esophageal eosinophilia, both of which persist despite prolonged treatment with proton pump inhibitors (PPI). Eosinophilic inflammation is absent in the stomach, small intestine, and colon.¹ The diagnosis of EoE is not based on one single marker (eg, number of eosinophils in the esophagus), but rather, on several clinical and pathologic features. This comprehensive definition is the guideline for the diagnostic work-up and for the choice of the diagnostic procedures in a patient who has suspected EoE.

EPIDEMIOLOGIC FEATURES AND DEMOGRAPHIC CHARACTERISTICS

Previously considered a rare curiosity, the startling prevalence of adult EoE has reached almost epidemic proportions. One prospective long-term study performed in Switzerland showed that the prevalence of adult EoE increased during a 19-year period from an initial 2, to a final 43, patients per 100,000 inhabitants. These data illustrate that EoE is indeed of general relevance because about 1 individual in 2500 is affected. In addition, the actual incidence in this area is 2.39 newly diagnosed cases per 100,000 inhabitants per year¹⁰ (personal experience). But is this a true rise in the incidence or simply an increased awareness of the disease? Because this study was conducted in a demographically stable, well-defined indicator area, under population-based conditions and unchanged recording practices, the data likely reflect an actual increase in EoE cases, and not just an enhanced awareness of the disease.

EoE shows a strong predilection for the male gender; among the reported cases, more than 70% involve men.¹¹ In a national database analysis, Katzka and colleagues¹¹ demonstrated that EoE occurs in all age groups; their patients ranged in age from 1 to 98 years, but the disease tended to peak in the fifth decade of life.

PRESENTING SYMPTOMS IN ADULTS WHO HAVE EOSINOPHILIC ESOPHAGITIS

Important clues can be found by taking a careful history that focuses on esophageal-related and upper abdominal symptoms, atopic diseases, and family history of both. As in many other diseases, the presenting symptoms have age-related differences. In contrast to children who experience food refusal, failure to thrive, and pain, EoE in adolescents and adults causes a rather narrow spectrum of symptoms, with the typical complaint being dysphagia for solids.^{12,13} In some patients, difficulty with swallowing occurs occasionally and then increases over time, whereas others report an abrupt onset of symptoms. Patients can often locate precisely the critical, most affected segment of the esophagus. In general, symptoms are more prominent and the swallowing disturbances more pronounced when the ingested food's consistency is dry or rough, or when the patient eats quickly. The dependency of the dysphagia on the food consistency indicates a probable mechanical problem with bolus transport through the affected esophagus, and not an immediate allergic reaction or spasm induced by the release of eosinophil granule proteins.

During the course of the disease, more than one third of untreated patients who have EoE will experience long-lasting food impaction that will require endoscopic bolus removal.⁹ In a recent report from a private practice setting, Desai¹⁴ found that 17 of 31 (55%) adults presenting with food impaction were found to have EoE. EoE is most likely the leading cause of food impaction, at least in younger male patients.

A few patients experience retrosternal pain that is either spontaneously occurring, or induced by ingesting alcohol (eg, white wine) or acidic liquids (eg, orange juice)

(author's personal experience). EoE retrosternal pain more closely resembles that described for vigorous achalasia than for gastroesophageal reflux disease (GERD): it is neither ascending nor related to reflux of acidic or gastric contents. Typical GERD symptoms may appear during the long-term course of EoE as a result of the insufficient lower esophageal sphincter (LES) evoked by the chronic inflammation.¹⁵ Many adults have symptoms, including recurrent food impactions, for years (an average of 4 to 5) before a diagnosis of EoE is finally made.⁴

More than 70% of adults who have EoE have a history of atopic disease, mainly allergic diseases of the airways, such as seasonal rhinoconjunctivitis and asthma.¹ Finally, a family history may provide further information: Noel and coworkers¹⁶ found that in their series of 103 patients who had EoE, 73.5% had a positive family history for atopic diseases and 6.8% for EoE, and 9.7% had undergone esophageal dilation.

PHYSICAL EXAMINATION

In contrast to the conspicuous medical history, the physical examination of adult patients who have EoE is usually unremarkable¹ because of the anatomic inaccessibility of the esophagus during the physical examination and because EoE in adults seldom provokes systemic manifestations.

LABORATORY ANALYSES

Laboratory analyses of a patient who has EoE have no more than a complementary value. Unfortunately, we still do not have reliable, noninvasive markers, either for establishing the diagnosis or for monitoring the disease.¹ However, two routine laboratory methods may prove informative: Between 5% and 50% of adults who have EoE have a mild eosinophilia on their differential blood count,¹⁷ although values seldom exceed 1500 eosinophils/mm³. A differential blood count may therefore provide supporting evidence for the presence of EoE, but it is by no means diagnostic. Whether the degree of the eosinophilia correlates with the disease activity is not yet elucidated. Furthermore, approximately 70% of patients who have EoE have elevated total IgE values.^{1,17} To date, no studies have been able to document whether total IgE can serve as a surrogate marker for disease progression or resolution, but some evidence indicates that, when compared with patients having normal levels, those who have high total IgE levels respond less well to corticosteroid treatment.¹⁸

ENDOSCOPIC FINDINGS

Although neither a pathognomonic endoscopic sign nor a typical pattern of abnormalities is associated with EoE, upper endoscopy is the first diagnostic step in the evaluation of an individual who has dysphagia.¹⁹ Many different endoscopic features are associated with EoE, the leading ones being longitudinal furrowing, white exudates, edema, longitudinal shearing, friability, crêpe paper mucosa, small-caliber esophagus, Schatzki ring, corrugated or ringed esophagus, and solitary rings.¹⁵ These signs usually appear in random combination in any given patient.²⁰ White exudates and longitudinal furrowing likely reflect acute inflammation, whereas crêpe-paper mucosa, corrugated rings, and strictures are likely a consequence of the chronic eosinophilic inflammation. All these signs are suggestive of the diagnosis of EoE, but the endoscopic suspicion requires histologic confirmation. Some early studies report normal-appearing mucosa in EoE.¹² However, as experience is gained in endoscopic identification of EoE, more endoscopists will be able to identify those subtle mucosal changes that were likely overlooked previously.

HISTOLOGIC FEATURES AND DIAGNOSTIC CRITERIA

Considering EoE as a clinicopathologic entity and according to its definition, diagnosis requires histologic confirmation: the esophageal biopsy shows a marked eosinophilic infiltration.¹ Under healthy conditions, the human esophagus is devoid of eosinophils.^{21,22} Despite the fact that an eosinophilic infiltration of the esophagus is a nonspecific sign that can be found in several other conditions,²³ finding a relevant number of eosinophils in the esophageal mucosa is highly suspicious for EoE. Experts still dispute the precise density of eosinophils required to confirm the diagnosis²⁴ because the infiltration seen in EoE is of a patchy nature and may even fluctuate during the course of the disease. Using an arithmetic model, Gonsalves and colleagues²⁵ have demonstrated that the selected threshold value (peak number of eosinophils per high-power field) and the number of biopsies taken for analysis determine the sensitivity of the combined “endoscopy–histology” method. Today, most experts agree that diagnosis of EoE can be established if a peak infiltration of at least 15 eosinophils per high-power field is found in combination with other subsidiary histologic findings and typical symptoms.¹ The additional histologic abnormalities suggestive for EoE include eosinophilic microabscesses, superficial layering, basal zone hyperplasia, and increased papillary size.¹ EoE exclusively involves the esophagus; gastric and duodenal biopsies are normal.

NATURAL HISTORY AND COMPLICATIONS OF EOSINOPHILIC ESOPHAGITIS

Despite the fact that our understanding of the natural history of EoE is still limited, it has become clear that this is a chronic disease whose course may be either chronic persistent or chronic relapsing.⁵ So far, no case of EoE with a superimposed premalignant condition or with a malignancy has been reported, but long-term follow-up is required to confirm this observation. The main concern is that a long-standing, untreated eosinophilic inflammation would evoke irreversible structural alterations of the esophagus, leading to fibrosis and angiogenesis, and result in thickening of the wall with abnormal fragility.^{5,26} Strictures are rarely reported in children, suggesting that this complication requires years of unbridled eosinophilic inflammation.³ This so-called “esophageal remodeling” may provoke several complications.

Acute food impactions are the leading complication of untreated EoE. Indeed, EoE was diagnosed in about 60% of adult patients referred for a diagnostic work-up of food impaction.¹⁴ During the course of their disease, more than one third of adult patients will experience long-lasting food impactions that require endoscopic removal.⁹ The risk for impaction depends primarily on the consistency of the food, and particularly problematic are dry rice and fibrous meat (eg, chicken or beef). This extremely disagreeable and frightening form of dysphagia is a sword of Damocles hanging permanently over almost all patients who have EoE. Food impactions are often the trigger for patients to consult a physician to perform a diagnostic work-up of long-lasting dysphagia. These unforeseeable events harbor several risks, such as retching-induced esophageal rupture (Boerhaave syndrome) or procedure-related perforation,⁹ which has the practical consequence that, in patients who have a long history of dysphagia, invasive procedures (eg, removal of impacted food or dilations) must be performed most delicately.

In addition to the leading symptom of “dysphagia,” typical reflux symptoms that respond to pharmacologic acid suppression may appear during the long-term course of EoE. In their case series, Remedios and colleagues¹⁵ found that among 26 adult patients who had EoE, 10 (38%) had coexisting reflux disease previously confirmed by pH monitoring. Furthermore, based on motility studies, the investigators found

that 8 of the 10 patients with coexisting reflux also had a reduced pressure in the LES. These findings suggest that, in EoE, the chronic inflammation can lead to an LES dysfunction, and thus to a clinically relevant, secondary reflux disease. However, our knowledge of the natural history of EoE is still fragmentary and further studies are urgently needed. Finally, it is only with a precise understanding of the natural course of a disease, including its inherent complications, that an informed decision for possible therapeutic interventions can be made. The natural course of EoE still awaits cracking.

THERAPEUTIC PRINCIPLES FOR ADULTS WHO HAVE EOSINOPHILIC ESOPHAGITIS

At least three reasons exist to treat an adult patient presenting with clinically and histologically confirmed active EoE: (1) to alleviate the diminished quality of life that the dysphagia evokes; (2) to prevent acute food impactions and their associated risks; and (3) to protect the esophagus from long-term sequelae. Nevertheless, just what the optimal treatment is for EoE has yet to be defined, and experience has been limited mostly to case series and small controlled trials.^{18,27} In adult patients who have EoE, topical and systemic corticosteroids, leukotriene receptor antagonists, immunomodulators, and dilation have proven efficacy, and PPI can reduce the often-present GERD-like symptoms,¹ whereas therapy with diet is still under evaluation.²⁸ To fulfill the diagnostic criteria for EoE, a treatment attempt with PPI acid suppression is considered almost mandatory. Although PPI may be useful for patients who have established EoE who have symptoms due to concomitant or EoE-induced GERD, it cannot be considered a primary therapeutic option for EoE.

Several clinical trials and many case series have demonstrated that systemic and topical corticosteroids are highly effective in resolving symptoms and signs of active EoE.^{17,18} A comparison of topical with systemic corticosteroids has shown no significant difference in the efficacy of these two forms.²⁷ In general, topical corticosteroids are used as first-line medications. They are well tolerated and, in most patients, clinical and histologic resolution is achieved within a few weeks. The drugs, either fluticasone propionate (Flonase, Veramyst) or budesonide (Rhinocort Aqua), are administered by mouth and can be divided into twice or four-times-daily doses. Most experts recommend starting with a high-dose induction treatment followed by a low-dose maintenance therapy. With the exception of oropharyngeal candidiasis, topical corticosteroids are almost free of side effects.¹⁸ However, when topical or systemic corticosteroids are discontinued, the disease generally recurs within a few months.^{3,18,27} The long-term management is still not defined and further studies are urgently needed to clarify treatment schedules and pharmacokinetic properties of topical corticosteroid treatment. The use of systemic corticosteroids should be limited to patients who have persistent symptoms and inflammation despite adequate dosage and correct application of topical corticosteroids.

At high dosages, leukotriene receptor antagonists, (eg, montelukast, Singulair), have been shown to induce symptomatic relief. However, their use has not been shown to affect the underlying esophageal eosinophilia significantly.²⁹ Like so much with EoE, the use of this drug for the treatment of EoE requires further investigation.

Novel biologic agents, such as monoclonal antibodies directed against interleukin-5 (eg, mepolizumab)³⁰ or tumor necrosis factor- α blocking agents (eg, infliximab, Remicade),³¹ present a unique opportunity for patients who have severe EoE refractory to standard therapies. However, these molecules await larger clinical trials and cannot be recommended for routine use at the present time.

Esophageal dilation is useful for patients whose symptoms do not respond adequately to medical therapy, mainly patients presenting with a functional narrowing of the esophagus.³² This condition may occur as a sequela of the chronic, untreated eosinophilic inflammation. Dilation encompasses a certain risk for mucosal tearing and frank perforation.⁹ Because the responsiveness of strictures cannot be predicted based on endoscopic findings, a therapeutic attempt with topical corticosteroids before performing dilation is highly recommended. With respect to the abnormal fragility of the EoE mucosa, an inspection of the esophagus should be done following dilation to assess the extent of possible laceration. Because dilation in patients who have EoE has to be performed subtly and less aggressively than in non-EoE stenoses, several sessions may be required before the patient reaps benefits from this therapy.

OUTLOOK

Even though our understanding of EoE has increased enormously during the last decade, many issues remain unresolved. Indeed, our understanding of EoE's natural history is still limited and we have no predictive factors to identify patients who are at risk for developing esophageal remodeling. We need indicators for distinguishing between pure EoE and GERD-associated esophageal eosinophilia, and we need non-invasive markers for monitoring disease activity. Future efforts must focus on defining long-term medical management and the still-controversial managing of patients refractory to standard therapies. Should one treat asymptomatic patients who have esophageal eosinophilia? Further joint efforts between clinical researchers and basic scientists addressing these issues are urgently needed to improve the lives of those ever-increasing numbers of individuals affected with EoE.

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