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Review

Diagnostic approaches and treatment of eosinophilic esophagitis. A review article

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HIGHLIGHTS

- EoE is an eosinophilic influx into the esophagus epithelium.
- It is an allergic reaction of esophagus to food particles and allergens.
- Adults present with dysphagia and reflux-like symptoms whereas children with vague abdominal complaints.
- Clinical presentation, endoscopic findings and pathology determine the definitive diagnosis.
- Treatment starts with an elimination diet and followed by orally swallowed inhaled steroids.

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ABSTRACT

Eosinophilic Esophagitis (EoE) is a condition that involves eosinophilic influx into the esophageal epithelium. It affects both children and adults; Adults present with dysphagia whereas children with vague abdominal complaints. The clinical symptoms as well as pathologic features of EoE and gastro esophageal reflux disease (GERD) are similar. Since eosinophilia in the esophagus is a non-specific finding, the clinical presentation in conjunction with endoscopic findings and pathology, is crucial in determining a differential diagnosis. Infections such as parasites, allergic phenomenon, Crohn's disease, malignancies, medication, and chemotherapy are all associated with eosinophilia.

A primary endoscopic difference to note between EoE and GERD is that EoE often involves long segments of the esophagus, could be patchy or focal and frequently involves the proximal esophagus. GERD, however, typically involves the distal much more frequently than the proximal esophagus. Because of the similarity between them, GERD should be excluded by using high dose proton pump inhibitor (PPI) treatment or through evidence of a normal pH by esophageal testing, prior to treatment with an elimination diet or steroids. Until further research establishes different diagnostic tests and criteria, clinical and pathological response to therapy is considered to be the absolute confirmation of this diagnosis. The following is a more detailed discussion of this entity.

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1. Introduction

Forms of esophagitis have been recognized for hundreds of millennia. The Sumerians and Greeks have words describing this phenomenon. The romans used calcium carbonate for its treatment [1]. From the mix of milk, cream and antacids taken before the availability of histamine blockers in the mid-70s, to the later appearance of PPIs in the late 80s, more and more treatments have become common use for this entity. In an unusual chain of events in medicine, however, our real knowledge of the phenomenon was acquired after treatments were readily available, mostly due to fiber optic advances and wide use of endoscopy and biopsy of the esophagus which revealed pathology well beyond what was known beforehand.

Today with the advances in food technologies and widespread availability of cheap processed food products (possibly containing new and improved allergens), esophageal disease is more and more prevalent. Up to 37% of certain populations can suffer from esophageal symptoms on a weekly basis [2].

Inflammatory diseases of the esophagus are numerous and may include: infections such as Candida; allergic responses involving an eosinophilic infiltrate; medication-induced, for example Bisphosphonates; reflux-induced; infiltration by lymphocytes; and bullous skin disease extensions into the esophagus. This review will focus on eosinophilic esophagitis, which is a diagnosis made more and more in clinical practice. It is important to remember that EoE is different from eosinophils in the esophagus, which is a non-specific pattern that can happen because of a variety of non-connected etiologies.

2. Definition

EoE is a chronic immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation [3]. EoE is used for abbreviation of eosinophilic esophagitis since erosive esophagitis is abbreviated as EE. There should be gastrointestinal eosinophilia limited to esophagus causing characteristic symptoms, while other etiologies for eosinophilia have been ruled out, for physicians to refer to it as EoE. Overall the pathogenesis involves genetic, environmental and host immune system factors interacting as will be discussed.

3. History and epidemiology

There are reports from the 60s and 70s that describe entities that could have possibly been cases of EoE. These patients with multiple esophageal rings were classified as GERD complications based on their biopsies showing basal zone hyperplasia, papillary lengthening and intraepithelial eosinophils [4]. However, these are not common findings in GERD. The response to acid suppression therapy was nowhere as successful as GERD in these patients. Severe complications such as deep mucosal tears or occasional perforations usually followed [5]. Interestingly, these cases were considered to be “extreme” GERD cases and end of GERD spectrum. The true pathological identification of the entity happened in the 90s and separated it from GERD.

EoE has been reported everywhere in the world other than the African continent, albeit there are regional variations depending on socioeconomic and climate zones. Lower socioeconomic populations in cold and arid areas seem to be more prone to EoE. The incidence of EoE is increasing, undeniably from widespread knowledge of the entity, but also because cheap, processed, modified food is universally accessible and abundantly overused. Prevalence has been estimated to be about 12.8–55 per 100,000 [6] with most of, many of affected adults being men in their 20s and 30s. EoE is predominantly associated with food and environmental allergies, asthma, atopy and celiac disease.

4. Genetics

Family clustering has been noted in some 30 families with EoE [7]. A positive family history can be found in at least 7% of the affected. There is a strong sibling ratio and the risk is 50-fold for siblings compared to general population. The risk is even higher in patients with advanced stenotic EoE.

Several genetic markers have been identified. Although some are common genetic variants, others appear to be specific for EoE. Eotaxin-3, 5q22 (involving gene encoding Thymic stromal lymphopoietin or TSLP), filaggrin gene, transforming growth factor or TGF receptors have been associated with EoE [8]. The earliest works revealed dysregulated expression of 1% of the genome constituting an EoE genetic signature. RNA sequencing on esophageal biopsies showed long-noncoding RNAs. EoE susceptibility locus was also found at 5q22 (related to TSLP coding) and 2p23 (related to a protein expressed in esophagus). 2p23 is upregulated in EoE and induced by IL-13 in esophageal epithelial cells.

Although these are helpful clues in our understanding of the disease, they really don't give us an exact insight into why this phenomenon is happening. Many of these abnormalities have been reported in other pathologies as well.

A 96-gene diagnostic panel based on a study of EoE biopsies and genetics have been produced and is commercially available. It is in effect a genetic testing for EoE molecular transcriptome and might

have both diagnostic and management value in future especially for separating active and inactive disease.

5. Clinical picture and diagnosis

Diagnosis is one of exclusion and it is not unusual for patients to experience at least 6 years of symptoms before being diagnosed appropriately. Symptoms initiate history and physical, extensive diagnostic work-up and endoscopy with biopsy.

History is extremely useful. Solid food dysphagia (that might be intermittent) is the most common symptom, followed by food particle impaction, atypical chest pain, epigastric discomfort and vomiting. In children the picture is somewhat different and includes abdominal pain, feeding refusal, weight loss and failure to thrive. The physical exam is usually not significant unless late complications have happened. Labs are also of limited value and show non-specific inflammation and elevated IgE levels. Mild peripheral eosinophilia is seen in many patients as well, but significant peripheral eosinophilia is absent. Barium studies of the esophagus can show strictures and some other findings, but they are more useful in ruling out other causes of symptoms.

Endoscopy will show a variety of findings: Linear furrows in 48%, stacked circular rings in 44%, attenuation of the sub epithelial vascular pattern in 41%, whitish plaques (eosinophil micro abscess) in 27%, strictures in 21%, reduced diameter of the esophagus in 9% [9], and mucosal tear or esophageal perforation in more advanced presentations. Biopsy and characteristic pathology in the absence of other causes of eosinophilia will yield the diagnosis. Sensitivity of endoscopic findings for EoE is low but specificity high (91% for rings, 94% for white plaques, 95% for linear furrows and strictures). Sensitivity of biopsy will increase with the number of sites biopsied, especially sites involving furrows and exudates. Some patients have no endoscopic findings, but the biopsy (that should be done regardless) will show the characteristics of EoE.

Eosinophils can be seen in other diseases as well but differentiating should not be very difficult. GERD will respond to PPI treatment. 24-hour PH monitoring of esophagus might be warranted in some GERD cases. Parasites and fungal infection have other characteristic in history and physical and respond well to their specific treatment after lab tests confirmed them. Crohn's disease, connective tissue disease and vasculitis have extra-esophageal manifestations and more widespread symptoms than the localized esophageal disease of EoE. Drug side effects can be pinpointed to the start of medicine and easily treated with withdrawing the offending agent. Bullous dermatosis has unique skin lesions. Celiac disease has strong abdominal presence and symptoms.

Based on endoscopy, there are two subtypes of EoE: The inflammatory one with transient rings, furrows and plaques and the fibro stenotic one with fixed rings and strictures. The latter one is unusual in children (Fig. 1).

American college of gastroenterology defines EoE when there are symptoms of esophageal dysfunction with esophageal biopsy showing eosinophil-predominant inflammation (more than 15 eosinophils per at least one high power field of the microscope). Eosinophils should be in esophagus only and persist despite 2 months of proton pump inhibitors. All other possible causes for the presence of eosinophils should have been ruled out as well [10].

6. Pathology

The esophagus is normally devoid of eosinophils but can recruit them in response to stimuli. Usually two to four biopsies from distal esophagus plus two to four from proximal and midsection are needed for diagnosis. This is particularly important since EoE is a patchy disease and might not be present in all sections. Gastric and duodenal biopsies are also frequently done to rule out eosinophils in those places that might have migrated to esophagus and are not representing true EoE. Biopsies should be done after 2 months of PPI. As mentioned, the presence of more than 15 eosinophils per at least one high power field of the microscope is the key. The eosinophils could be in the form of micro abscesses, superficial layering, diffuse sheets or extra-cellular granules (Fig. 2). Other inflammatory cells can also be seen. Pathology usually correlates poorly with the clinical picture. During treatment with steroids, the absolute count of eosinophils will decrease, but this may not translate into clinical response or symptom improvement.

7. Immunopathology

The esophagus is the one part of the gastrointestinal system devoid of eosinophils; therefore, its presence defines pathology. EoE Pathology could have been initiated with a pure immunoglobulin mediated response to environmental antigens in genetically-predisposed individuals. About 75% of people with EoE have atopy and evidence of other food/aero allergens as well. This is magnified by the fact that elimination diets are first line treatment for EoE. Despite the presence of eosinophils in the esophagus, their peripheral presence is very limited signifying a potential esophagus-regulated mechanism for this phenomenon.

Also of significance is the T cell immunity through different interleukin expressions. Interleukin 5 in particular seems to mediate eosinophil-induced esophageal remodeling and collagen deposition.

8. Differential diagnosis

A variety of diseases can mimic EoE and vice versa. GERD is the most common, followed by different forms of allergies, parasites and fungal infection, congenital rings, Crohn's disease, connective tissue disease and vasculitis, drug side effects and hypersensitivity, bullous dermatosis, achalasia, carcinoma, and celiac disease [11].

EoE is a differential diagnosis in young males with persistent dysphagia, severe, unresponsive GERD or food impaction. History of allergy and **atopy** as well as late manifestations such as ring formation can also point in the direction of EoE.

9. Treatment

9.1. Dietary modifications

Food allergy is recurrent and predictable immune response upon ingestion of a food antigen and is in very close relationship with EoE as mentioned. There are several methods for elimination of allergens and antigens from diet: 1) Directed elimination diet, uses skin prick testing and atopy patch testing to identify potential allergens and then remove them from the diet. 2) Empiric elimination diet gets rid of the foods that cause the most allergies in the population. Milk, egg, soy, wheat, peanuts and fish are the “big six” of the food allergy world and will be eliminated. 3) Elemental diet (amino acid based), avoids all potential allergenic food peptides altogether.

Each method has its own advantages and disadvantages. Direct elimination is promising, but not in general use and is somewhat cumbersome and costly for individual. Identification and avoidance of specific allergens can be a challenge, but over time many patients will realize which foods are triggering their symptoms and will avoid them by experience. Empiric elimination seems logical, but data show that peanut and fish might not be as important in EoE as with other allergies and other foods such as meat and grain might

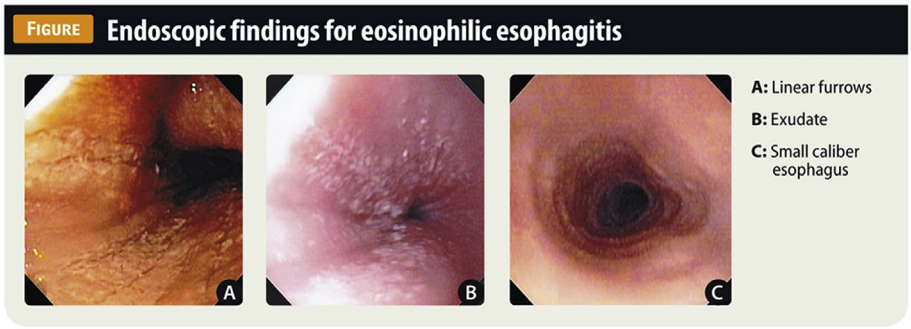

Fig. 1. Endoscopic findings. Reproduced with permission from Susan Schuval MD, David Gold MD, Contemporary pediatrics. December 2013.

be more problematic in this regard.

Elemental diet is extremely effective (90% in children) but will narrow the dietary choices of its practitioner to an almost torturous spectrum. Elemental diets decrease allergy exposure and should be first line treatment in both adults and children, if they can cope with it. Since EoE is associated with different allergies, this elimination diet will help at the source [12]. A problem can arise from over protection that might cause some nutritional deficiencies, but this can be addressed if symptoms are under control otherwise.

9.2. Acid suppression

GERD and EoE have a close relationship. GERD may mimic esophagitis, coexist with it or contribute to it. EoE can do the same to GERD. Acid suppression may help directly by treating co-existing GERD or indirectly by decreasing damage from acid over an injured esophagus. One third of patients with suspected EoE have good clinical and histological response to acid suppression alone, suggesting that GERD or an acid-suppression sensitive form of esophageal eosinophilia is responsible [13]. Many of these patients stay in remission with acid suppression therapy alone.

There are two possible explanations for the role of PPIs: Acid might cause damage to the mucosa and increased permeability allowing allergens to influx in. Anti-acids will prevent this cascade. The second possibility is that PPIs can reduce the level of key mediators of EoE such as eotaxin-3, interleukin 4 and 5 directly.

PPI in usual doses is sufficient for treatment purpose and no specific one is shown to be more potent than the others. Many patients will require long term suppression to avoid relapse. Pantoprazole, Lansoprazole, dexlansoprazole are the most bioavailable and achieve the highest plasma levels. Rabeprazole has a faster onset of action. Esomeprazole and omeprazole are also available and in case of the latter, over the counter. Once before bed dosing might be enough, but twice daily will have more pronounced effects.

9.3. Topical steroids

Swallowed steroids are usually helpful in treatment, although no formulation is preferred and no universal successful method has been recognized. Different people respond differently to steroids. Inhaled steroids such as Fluticasone and budesonide will be inhaled at the usual dose used for allergy and asthma (one or two puffs once or twice daily), into mouth, swallowed and with no food or drink intake or an hour (washing them off or interfering with them). 0.5 mg of Budesonide daily inhaled like this has yielded great symptomatic response.

Viscous steroids that are meant for rectal use in inflammatory bowel disease are also available and can be used at a higher price tag via oral swallowing when mixed with more tasteful solutions. Overall, however, patients seem to prefer the inhaled method more.

Many patients respond favorably, but many relapse as soon as steroids stops, which necessitates long term use of them. Chronic long term use of steroids regardless of route of use will cause adrenal insufficiency and other known complications. Worsening of symptoms during treatment might be a sign of infections developing due to steroids. Candida esophagitis is the usual suspect in this setting.

Role of systemic steroids is very limited to only severe cases precisely because of the frequent need for long term use, which can cause devastating side effects which are even more pronounced and faster appearing with systemic intake.

9.4. Leukotriene receptor antagonists and immunomodulators

Might have a place in treatment or even prevention of further damage. General antihistamines and cromolyn have no benefit in this disease. Montelukast and Mepolizumab (monoclonal antibody against IL-5) were initially promising but later yielded mixed results. IL-5 has a central role in eosinophil recruitment. Reslizumab is another IL-5 neutralizing antibody which should promises but not as significantly as hoped.

9.5. Esophageal dilatation

If there are rings or high grade strictures, especially when producing severe dysphagia, there is a need for dilatation of the esophagus. This treatment, however, will not affect the baseline inflammation. It should be done carefully, gradually and selectively

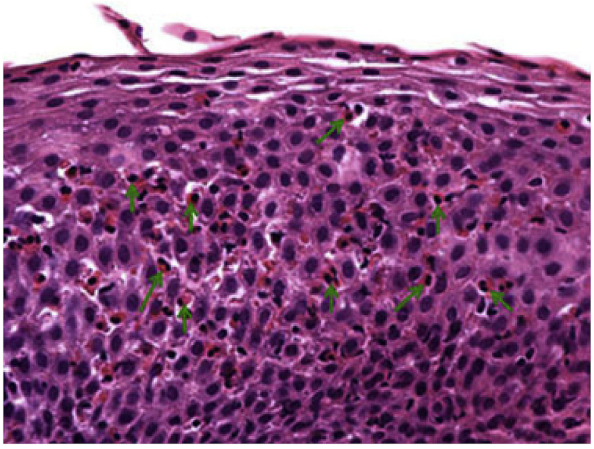

Fig. 2. Pathologic findings with prominent eosinophils (arrows).

since it can potentially cause mucosal tear or esophageal rupture. A very gradual increase of diameter of about 3 mm with each session to achieve an esophagus diameter of 15–18 mm is the goal. This is the least diameter that produces sustained symptomatic relief.

9.6. Surgery

Removal of esophagus in extreme cases is the end of treatment spectrum, but will happen very infrequently and mostly not due to symptoms but due to late stage complications such as rupture. Partial esophagectomy is preferred, if possible.

10. Prognosis

The natural history of the disease, with or without treatment, is not well known in part because it is a relatively newly discovered entity. Some people stay asymptomatic while others experience symptoms and progress into extreme esophageal narrowing. Many cases that are responsive to treatment will need long term suppression or else relapse might happen.

11. Pregnancy

The number of pregnant patients with EoE is increasing. No immediate guideline is available for management, but some authorities have used inflammatory bowel disease as pathology like EoE and studied its course in pregnancy as an example of how it might behave and should be treated [14].

It will be helpful to have knowledge on safety and risks of diets and steroids during pregnancy and nursing, effects of elimination diets on the fetus, use of endoscopy during pregnancy and so on. Also of interest would be to see if the natural progress of the disease will change with pregnancy or not.

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Author contribution

Only one author for this review who has done all the work.

Conflicts of interest

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