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Review Article

Eosinophilic Esophagitis

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Abstract

Eosinophilic Esophagitis (EoE) is a long-standing, relapsing immune-mediated esophageal disorder, facilitated by atopy, resulting in dysphagia and esophageal strictures. The prevalence has been leaping in the last few decades consistent with the enhanced understanding of the disease. It occurs in people from all ages but children and young males are especially affected. A wide spectrum of factors has been associated with it, including genetic and environmental risk factors. In atopic individuals, interaction of allergens with the esophageal epithelium generates a T-helper cells type2 driven immune response, which leads to the activation of inflammatory cytokines which in turn induce various genes causing formation and recruitment of eosinophils as well as mast cells setting in a chronic inflammatory process. Diagnosis is made on typical clinical, endoscopic and histological factors. Therapeutic modalities range from dietary restriction to corticosteroid therapy. Endoscopic intervention may be needed for patients presenting with esophageal strictures. Recently, biological agents have also been under trials for its treatment but there is no FDA approved drug therapy available as yet. It is a relatively new disorder that is constantly under evolution in terms of diagnostic and therapeutic fields.

Keywords: Eosinophilic Esophagitis; Dysphagia; Food Impaction; Esophageal Stricture; Atopic Disorder

Introduction

Eosinophilic Esophagitis (EoE) is a chronic multifactorial disorder of esophageal dysfunction mediated by an amplified immune response to allergic stimuli, leading to persistent eosinophilic inflammation and eventual remodeling of esophagus. Over the past three decades, EoE has evolved from a rare clinical entity to a well-known illness with gradually increasing prevalence throughout the world. Since it is a recently recognized disease, roughly in the early 1990s [1,2] a continuous growth has been observed in terms of its clinical diagnosis and appropriate therapeutic strategies.

Epidemiology

Eosinophilic Esophagitis has slowly emerged as a notable cause of upper gastrointestinal tract symptoms in individuals of all age groups. It has shown a bimodal tendency as most of the affected patients belong to either pediatric group or adults above 30 years of age [3]. According to a meta-analysis conducted in 2019, the incidence of EoE in children was 6.6/100000 person-years while that of adults was found to be 7.7/100000 person-years. The overall prevalence of EoE was estimated to be 34.4/100000 individuals with adults having a higher prevalence (42.2/100000) compared to that of children (34/100000) [4]. Studies have demonstrated a male predominance, with an estimated male to female ratio of 3:1 [5]. Geographical variation also has an impact on the prevalence of disease, as a greater prevalence is observed in the North America, Australia and Western Europe compared to that of Eastern countries [6]. The regional differences in prevalence point towards envi-

ronmental factors being an important etiology of the disease, urging further investigation.

Pathophysiology

Owing to the heterogeneity of EoE, the understanding of the disease pathogenesis is continuously evolving. The basic underlying mechanism seems to be disruption of esophageal epithelial barrier along with an exaggerated cellular immunity [7]. Antigenic proteins from ingested food trigger T-Helper cells type-2 (Th2) in the esophageal epithelium to stimulate secretion of IL-4, IL-5 and IL-13, each of these play a significant role in promoting inflammatory cascade in the esophagus. IL-13 disrupts esophageal epithelial barrier by both direct and indirect means. It decreases desmoglein and filaggrin, both of which are crucial for epithelial integrity. IL-13 induces the gene CAPNT4 to produce an enzyme Caplain-14 which cleaves desmoglein, hence increasing epithelial permeability [8]. IL-13 also produces a chemo- attractant, called Eotaxin, which recruits eosinophils into the tissue and causes mast cells hyperplasia eventually leading to collagen deposition and remodeling of esophagus. IL-13 also releases periostin which is actively involved in the remodeling of esophagus. IL-5 enhances eosinophils activity and prolongs their survival. Activated eosinophils secrete IL-19 which augments mast cells activation leading to local mastocytosis. Together, activated eosinophils and mast cells produce profibrotic factors such as Transforming growth factor-Beta 1 (TGF-B1) and Fibroblast growth factor-9 (FGF-9) which amplify fibroblast proliferation, collagen production, epithelial to mesenchymal transition and fibronectin formation. All this results in basal zone hyperplasia, lamina propria fibrosis, expansion of mucularis propria and impaired barrier function, collectively called esophageal remodeling. TGF-B1 also releases periostin which takes part in remodeling. Once remodeling ensues, if left untreated, it progresses to fibrosis and stricture formation consequently. Figure 1 summarizes the pathogenesis of EoE.

Figure 1: Summary of EoE pathophysiology.

Risk factors

A myriad of factors have been implicated in the pathogenesis of the disease. A complex interplay between ingested, cutaneous and aero-allergens as well as genetic mutations lead to a hyper-active immunity eventually causing these disturbances. As per Genome-wide association studies, the genetic variants involved in the inflammatory cascade genes include Thymic Stromal LymphoProtein (TSLP) and STAT6 which promote Th2 differentiation, CAPN14 which produces a proteolytic enzyme Caplain-14, CCL26 which encodes eotaxin, LRRC32 which secrets TGF-Beta binding proteins as well as EMSY which is responsible for transcriptional regulation [9]. Overexpression of these genes is found in patients with EoE. Notably, down regulation of DSG1 and filaggrin has been demonstrated, these genes take part in preservation of epithelial integrity [10]. Male gender and Caucasian ethnicity seem to have a predisposition to development of EoE [11]. On the other hand, the disease seems to be familial as brothers possess a higher risk of having it. Early life factors that may have an impact on disease predisposition include type of delivery, breast milk consumption and use of antibiotics in infancy [12]. Among environmental factors, population density, exposure to *H. pylori* infections, quality of nutrients as well as chemical modification of food may play an important role [13]. Pollens season, cold or dry climate have also been linked with the disease [14]. Patients receiving oral immunotherapy are also more prone to having EoE [15]. Changes in esophageal microbiome may pose an additional risk [16]. A greater incidence of concurrent atopic disorders has been observed in EoE patients. Yet, contrary to the common belief, EoE is not an IgE mediated phenomenon, it has rather been associated with IgG-4 disease [17]. However, immune-staining of biopsy samples with IgG4 has not been fruitful. Diseases having a strong affiliation with EoE include GERD, Celiac disease and Inflammatory bowel disease [18]. EoE may be a part of other

systemic disease which include Ehlers-Danlos syndrome, Severe Atopy syndrome and Loeys-Dietz syndrome [19].

	Genetic Factors	Environmental Factors	Associated Conditions	Others
1	TSLP-causes Th2 differentiation	Allergens exposure (Food, Air, Skin)	GERD	Male gender
2	CAPN14-produces Caplain14	*H. pylori* infection	Celiac Disease	Caucasians
3	CCL26-encodes eotaxin	Breast milk	IgG-4 disease	Siblings
4	STAT6-Th2 development	Early birth	Severe Atopy Syndrome	
5	LRRC32-TGF-B binding protein	Use of antibiotics in infancy	Autoimmune disorders: -Inflammatory bowel disease -Rheumatoid Arthritis -Multiple Sclerosis	
6	EMSY-Transcriptional regulation	Oral immunotherapy		
7	FILAGGRIN-Squamous epithelium calls differentiation	Dense population	Connective tissue: -Ehler Danlos syndrome -Marfans syndrome -Loeys-Dietz syndrome	
8	DSG1-produces Desmoglein1	Gut Microbiota		
9		Climate changes	Hereditary: -Netherton syndrome	

Table 1: Lists down all the risk factors associated with EoE.

Clinical presentation

The clinical manifestation of EoE is greatly variable depending upon the age of patient. In early years of life, EoE may present with nausea, emesis, abdominal pain, feeding difficulties or failure to thrive. In later childhood, children may complain of heartburn, chest pain or parents may give history of peculiar eating habits such as excessive chewing, slow and picky eating and increased fluid intake during meals [20]. On the other hand, adults present with dysphagia, recurrent food impactions, odynophagia, chest pain or regurgitation. According to a study done on patients undergoing upper gastrointestinal endoscopy for various reasons, EoE was detected in 1 - 8% of patients with heartburn [21] and about 6% of patients with non-cardiac chest pain [22]. In severe cases, patients may land in emergency department with esophageal perforation (Boerhaave's syndrome) secondary to food impaction [23]. In recent years, EoE has been identified as the most common cause of recurrent food impactions. It is imperative to elucidate personal and family history of other atopic diseases.

Figure

Diagnosis

EoE is diagnosed on the basis of combination of clinical, endoscopic and histological features. As per guidelines, before establishing a definite diagnosis of EoE, it is crucial to exclude other possible causes of eosinophilia in esophagus [24]. For correlating clinical features with the diagnosis of EoE, several symptoms scoring tools have been introduced and validated. For pediatric population, a Pediatric Eosinophilic Esophagitis Symptoms Score (PEESSv2.0) has been proven to be quite effective [25]. This scoring system was developed by the University of Cincinnati and it remarkably cor-

relates clinical symptoms with histological findings. Whereas for adults, Eosinophilic Esophagitis Activity Index [26] successfully exhibits correlation between clinical manifestations, histological features and outcomes of disease. Documentation of symptoms frequency, intensity and chronicity is crucial. These scoring systems aid in accurately grading symptoms as well as in the assessment of disease over longer period of times and in the evaluation of effectiveness of treatment.

Endoscopy

Up until now, none of the non-invasive markers have been victorious in diagnosing EoE. Therefore, upper gastrointestinal endoscopy is the diagnostic investigation of choice. It is essential for both the evaluation of gross endoscopic features as well as for the collection of biopsy specimen from esophagus. In a patient with relevant history of dysphagia, esophageal biopsy is important as mucosa may appear normal in about 5% of patients. Frequently noted endoscopic features in adults include linear furrows (80%), circumferential mucosal rings (64%), small caliber esophagus (28%), whitish exudates (16%) and strictures (12%) [27]. While in children, endoscopy often reveals normal mucosa (32%) or linear furrows (41%), exudates (15%) and mucosal rings (12%) [28]. A particular resistance is felt while taking out biopsies from esophagus along with mucosal tenting, called the esophageal 'pull' sign, this is another marker for esophageal remodeling and highly specific for EoE. Recently, a novel endoscopic sign has been demonstrated to have great specificity towards EoE. A protruded mucosal lesion between the longitudinal mucosal furrows called 'the caterpillar sign' has the potential to become a reliable indicator of EoE in future. In order to grade and monitor disease activity, a standardized reference score was formulated based on endoscopic findings called the Endoscopic Reference Score (EREFS). It incorporates additional endoscopic features such as feline esophagus, crepe paper esophagus and strictures, for the diagnosis as well as assessing disease severity. Severe studies have validated this as a useful tool for the diagnosis of EoE.

Histology

Identification of typical histological features remains the gold standard for the diagnosis of EoE. On a background of pertinent symptoms, esophageal epithelium featuring greater than or equal to 15 eosinophils per high power field (hpf) constitutes the diagnosis of EoE. Since EoE has a patchy distribution, it is recommended to take multiple biopsy specimens from proximal and distal esophagus, preferably at least three samples from each region. This improves the diagnostic yield of tissue specimen. Other commonly encountered histological features include epithelial hyperplasia, sub-epithelial fibrosis, presence of eosinophilic microabscesses, spongiosis (intercellular edema) and eosinophils degranulation. For characterization of all important histological features, EoE histologic severity scoring (HSS) index has recently been devised and validated. Disease activity can be assessed using HSS to help strategize individualized treatment plan.

Other diagnostic modalities

In children, reluctance may be noted towards standard endoscopy due to the risk of sedation related adverse effects, considering the fact that such interventions are needed repeatedly over the course of treatment. In such circumstances, a good alternative may be trans-nasal endoscopy which does not require sedation and the duration of procedure and post procedure recovery is relatively shorter. Endoscopic ultrasonography may also be used for assessment of thickness of esophagus and EoE associated fibrosis. Dysfunctional esophageal epithelial barrier leads to dilation of intercellular spaces, which is inversely proportional to the esophageal mucosal impedance (MI). Measurement of MI is a tool that might be used to judge esophageal integrity and hence, activity of EoE. As per a study, patients were diagnosed with EoE using mucosal impedance, with 90% sensitivity and 91% specificity. Esophageal fibrosis is an inevitable consequence of EoE, characterized by decreased esophageal distensibility, that may not always be picked up by standard endoscopy. Impedance planimetry is a relatively newer technique that measures distensibility of esophagus through an orally passed catheter called Endoscopic functional luminal imaging probe (endoFLIP). This approach has the potential to become an excellent biomarker for the estimation of EoE progression.

Since endoscopy is an expensive and invasive procedure, non-invasive diagnostic modalities have been under constant scrutiny. The idea of making a diagnosis of EoE by molecular techniques is fascinating. The endoscopic diagnostic panel (EDP) is a molecular tool that can identify the expression of 96 dysfunctional genes involved in the pathogenesis of EoE. The sensitivity of EDP is around 96% and specificity is as high as 98% for the diagnosis of EoE.

Furthermore, it can also risk stratify patients by classifying them into three endotypes. Capsule-based technologies, such as the Cytosponge and esophageal string test, have shown good utility in assessment of esophageal inflammation and eosinophil infiltration respectively. Broadly, these both are minimally invasive techniques in which these capsules are introduced to the gastrointestinal tract and then withdrawn, bringing back a collection of esophageal cells for analysis. Another approach called tethered confocal endomicroscopy capsule may prove to be successful in recognition of esophageal inflammation. It is an optical imaging technique that imparts contrast depth-resolved cellular information from the tissue. If not for primary diagnosis, these modalities may be used for the evaluation of treatment response, thus eradicating the need for repeated endoscopies.

Figure 2: Summarizes the diagnostic features of EoE.

Treatment

Treatment of EoE revolves around halting the exposure to atopic factors by dietary modifications and altering the course of disease by drugs and use of endoscopic dilation in case of complications such as esophageal strictures, often referred to as the three 'Ds' of treatment (Diet, Drugs, Dilation). The goal of therapy is to control the disease characterized by alleviation of symptoms, reduction of esophageal eosinophils < 15 Eos/hpf, reversal of epithelial fibrosis and prevention of esophageal remodeling. Once remission is achieved, long term maintenance therapy is planned based on the symptoms of patients, as recurrence is common after treatment cessation. Instead of a step by step approach, a combination of therapies is often required to attain treatment endpoints.

Dietary therapy

In order to avoid exposure to dietary allergens, certain dietary therapies have been suggested and validated. Currently, the three distinct choices available are elemental diet, empiric elimination diet and allergy testing guided elimination diet.

Elemental diet is an amino-acid based formula that is devoid of all dietary antigens related to EoE. A meta-analysis demonstrated efficacy of elemental diet in 90.8% cases while proving its superiority over elimination diet. In other studies, elemental diet successfully achieved complete remission in children and in 80 - 90% of adults. Despite this, a substantial drop out rate was noted due to difficulties associated with elemental diet like poor palatability, high cost and psychological effects related to the lack of variety of food.

Due to obstacles related to elemental diet, the concept of elimination diet was put forward. Elimination diet involves avoidance of potential foods that may induce EoE. The 6-food elimination diet (SFED) is a well-known dietary therapy that is commonly used for the management of EoE. Gluten, milk, soy, eggs, nuts and sea-food have been strongly implicated as common triggers for EoE. SFED begins with absolute elimination of these six foods, with careful reintroduction of each food once remission has been achieved. Elimination diet was proven to be as effective (67.2%) as corticosteroid therapy (63.3%) as per a meta-analysis. However, it may have an impact on patient's quality of life as avoiding the most common daily life foods may become very stressful. Therefore, a step-up elimination diet is probably more favourable in terms of patient's tolerability, called the 2-4-6 elimination strategy. A major drawback of elimination dietary therapy is the need of endoscopy at regular intervals to ascertain the response to therapy during the food re-introduction phase and to recognize specific food triggers. The order of reintroduction of food is still under active research.

Another viewpoint is elimination of foods that trigger EoE, identified by food allergen test such as the skin-prick test and atopy patch test. This approach may be easily tolerable for the patients but its efficacy is not comparable to the other dietary therapies. A retrospective study showed histological response in only 3% of

children who adapted to food elimination based on positive allergy tests results, while limited response was observed in adults. However, a systematic review and meta-analysis is underway in determining its reliability and feasibility.

Pharmacotherapy

As of now, no FDA approved drug therapy exists for EoE. Due to a close relationship between GERD and EoE, proton pump inhibitors (PPI) have been extensively used for the treatment of EoE. PPIs exert a protective effect on esophageal epithelial barrier by reducing acid exposure alongside an anti- inflammatory effect. A wide variability is observed in response to PPI therapy, from 30% to 70%. Based on response to PPI-therapy, EoE has been classified into PPI-Responsive EoE and PPI-Resistant EoE. Although the underlying mechanism is unclear, but young age, low BMI and elevated peripheral eosinophil count have been associated with reduced response to PPI. An initial dose of 40 mg PPI twice daily in adults or 1 mg/kg/dose in children is recommended. However, the value of PPI in the treatment algorithm of EoE is still evolving. In patients with PPI-responsive EoE, expression of KCNJ2 gene was found to be lower. If this gets validated, this genetic testing could potentially serve as a screening test before commencing PPI-therapy.

An effective medical therapy is corticosteroids as they reduce inflammation and prevent disease progression. Several randomized control trials (RCT) have demonstrated that swallowed topical corticosteroids (TCS) like fluticasone, budesonide and ciclesonide are greatly effective in improving clinicopathological outcomes of EoE. It was illustrated that TCS are safer and have the same efficacy as systemic steroids. These are swallowed in a viscous vehicle at an initial dose of 1 mg (Budesonide) or 880 mg (Futicasone) twice a day. Due to chronicity of disease, relapse is a common occurrence after discontinuation of treatment and long term therapy is mostly required. In such cases, half dose of the induction therapy seems to be a reasonable approach. Factors suggesting need of long term maintenance therapy includes small caliber esophagus, stricture formation, recurrent food impaction, early relapse after treatment cessation, comorbidities enhancing risk of endoscopy or dilation, history of spontaneous or dilation related perforation along with travel history to areas where there is a higher risk of food impaction. Adverse effects related to TCS therapy are oral or esophageal candidiasis and rarely, adrenal insufficiency. Lack of histological response may occur in 5 - 40% of patients on TCS. In patients who do not respond well, non-compliance and incorrect administration must be ruled out before labeling it as refractory disease.

Since EoE is an immune-mediated disorder with inflammatory cytokines playing a major role in disease pathogenesis, monoclonal antibodies against interleukins have been under evaluation for achieving remission in patients refractory to steroid therapy. Dupilumab is a human monoclonal antibody that inhibits signaling of IL-14 and IL-13. A phase-II double blind, RCT demonstrated that dupilumab significantly diminishes clinical symptoms and improves histological findings. IL-13 has a crucial role in the disruption of esophageal barrier. QAX576 is a humanized monoclonal antibody that functions by inhibiting secretion of IL-13 by T-lymphocytes. A recent RCT on QAX576 showed histological response but no significant clinical response was noted. A recombinant humanized monoclonal antibody against IL-13, RPC4046 showed reduction in clinical, endoscopic and histological scores. A recent trial showed that RPC4046 as a long term maintenance therapy was safe, effective and well-tolerated. Mepolizumab, a humanized anti-IL5 antibody demonstrated good endoscopic and histological response without any noteworthy clinical improvement.

The role and mode of interval monitoring is not very clear and is usually dependent on primary physician's discretion. Most practitioners recommend surveillance endoscopy at 8 - 12 weeks after initiation of therapy for assessment of endoscopic and histological response.

Dilation

In case of structural alterations, manifesting as persistent dysphagia or recurrent food impactions, esophageal dilation with endoscopic balloons or bougienage is the therapy of choice. Although it provides long-term relief in symptoms, dilation has no impact on chronic inflammation or course of disease. It is a relatively safe and well-tolerated procedure with complication rate as low as < 1%.

Conclusion

EoE is a local clinicopathological entity that has only recently become known and its natural course and long term consequences are still uncertain. It can affect anyone although its prevalence is higher in children and young male patients. High suspicion index is crucial for disease diagnosis. Exclusion of secondary causes of eosinophilia is imperative. Prognosis is not very well known but life

Figure 3: Summarizes the treatment algorithm that may be followed in EoE.

expectancy is unaffected. Further research is vital to understanding the etiology and pathophysiology of disease in detail and to discover new non-invasive diagnostic modalities. Elimination diet and Topical corticosteroids are pretty effective and the advent of biological agents has added a great deal to the treatment spectrum. However, randomized control trials are needed to prove their efficacy and to gain FDA approval. The results of ongoing clinical trials are eagerly awaited.

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