Chapter

Eosinophilic Esophagitis in 2021

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Abstract

Eosinophilic esophagitis also known as asthma of the esophagus is a food-related allergic disorder of the esophagus widely distributed all over the world. The incidence and prevalence of eosinophilic esophagitis have been increasing over the last few decades. The pathogenesis of this entity is now better understood and three distinct endotypes have been defined for better management strategy. Diagnosis is made on the basis of clinical symptoms followed by endoscopy with biopsy. Drugs, diet and endoscopic dilation are the current modalities of treatment. IL-4 and IL-13 inhibitors have been found to be promising in clinical trials.

Keywords: eosinophilic esophagitis, asthma of esophagus, dysphagia, food bolus impaction, esophageal eosinophilia, esophageal stricture

1. Introduction

Eosinophilic esophagitis (EoE) is a chronic immune/allergy mediated disease of the esophagus characterized by esophageal eosinophilia (presence of ≥15 eosinophils/high power field in at least 1 esophageal biopsy.), esophageal dysfunction (dysphagia, food impaction) and characteristic endoscopic features [1]. To establish the diagnosis, other causes of esophageal eosinophilia must be excluded. In 1989, EoE was first recognized as a distinct clinical entity by Attwood et al. [2]. Now there is an epidemic of EoE in the western world. EoE is increasingly being recognized and diagnosed in our clinical practice both in the acute and chronic settings. EoE has distinct clinical epitopes, diagnostic and treatment protocol. The epidemiology, pathogenesis, pathology, clinical feature, investigations, management and prognosis will be described in this chapter.

2. Epidemiology

The disease is more common in Caucasian population with a male to female ratio of 3:1 [3]. Eosinophilic esophagitis has also been seen in African Americans, Asians and Hispanic population. The disease is increasingly being recognized over the last few decades. The current incidence is 5 to 10 cases per 100,000 population, and the current prevalence is 0.5 to 1 case per 1000 population in North America, Europe and Australia [4]. The disease can affect both children and adults. In adults, EoE is more commonly seen in males than in females and the average age of patients with EoE is between 30 and 50 years. Most of the patients with EoE have personal history of allergic disorders like bronchial asthma, allergic rhinitis, allergic conjunctivitis or food allergy.

3. Pathogenesis

Exposure of the esophagus to food and aeroallergens in genetically predisposed individuals may initiate the process of eosinophilic esophagitis although the exact mechanism is currently unknown [5]. Foods most commonly implicated in EoE are: Milk, egg, wheat, soy, peanuts, beans, rye and beef. Genomewide association analysis (GWAS) suggested that CAPN14 at 2p23 locus is upregulated after epithelial exposure to interleukin (IL)13 [6]. Recently, epithelialderived cytokine thymic stromal lymphopoietin (*TSLP*) gene at 5q22 locus has been identified as a candidate gene in

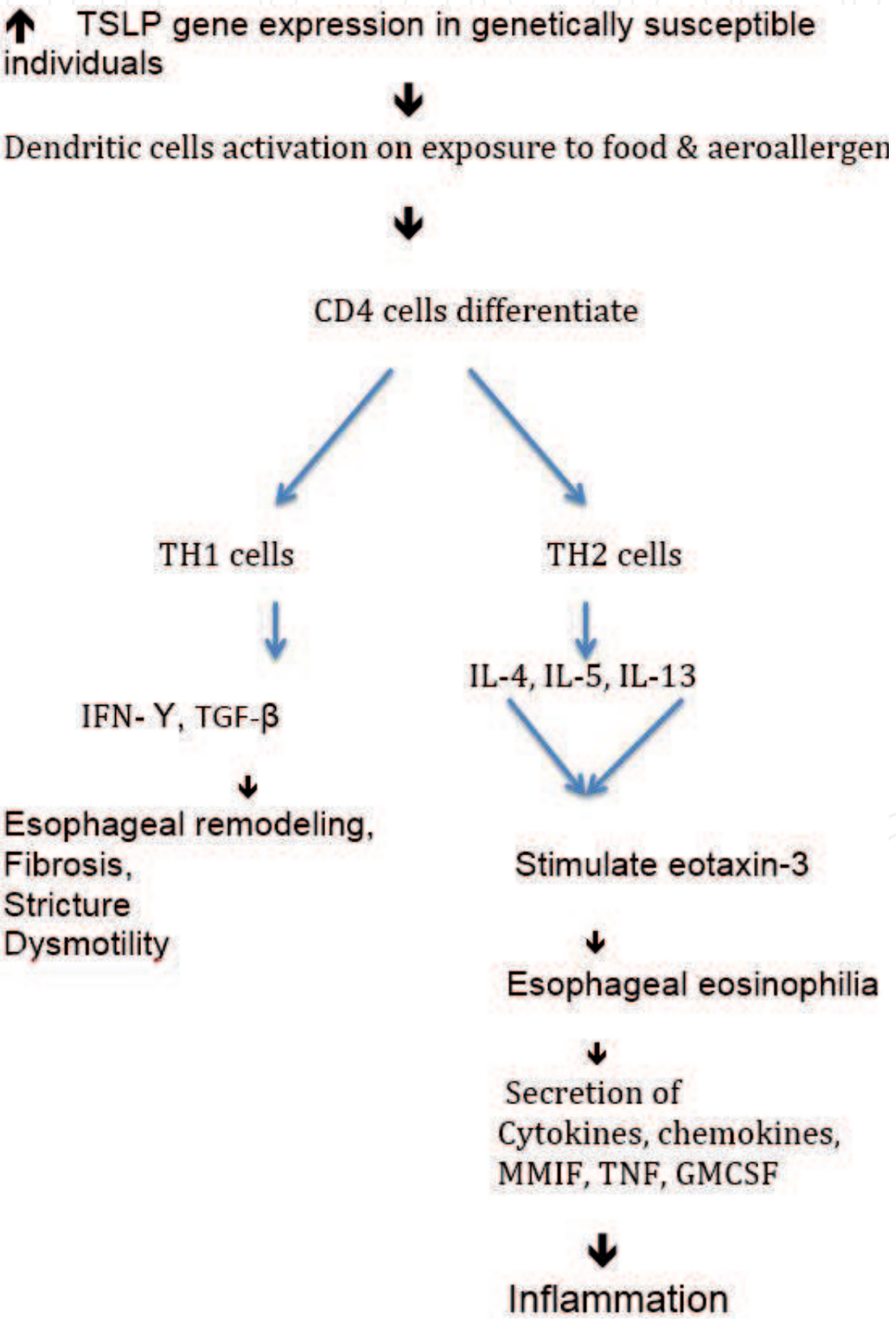

Figure 1.
Pathogenesis of EoE.

a multicenter GWAS. There is an increased expression of TSLP in patients with EoE. TSLP activates dendritic cells (antigen presenting cells). Food allergen is initially recognized by antigen presenting cells which differentiate CD4 cells into TH1 cells and TH2 cells. TH1 cells secrete interferonγ (IFN-ϒ) and transforming growth factorβ (TGF-β). TH2 cells secrete IL4, IL5 and IL13. There is also single nucleotide polymorphism (SNP) in this TSLP receptor gene in male patients with EoE. This gene is found on the pseudoautosomal region on Xp22.3 and Yp11.3. This finding may explain increased prevalence of EoE in male patients. There is also a suggestion of second hit for the development of EoE. Tolllike receptor3 (TLR3) can recognize double-stranded RNA (found in some viruses) and can induce TSLP [7]. IL5 is responsible for eosinophilic infiltration, growth and survival. Eosinophils secrete various inflammatory cytokines and chemokines including macrophage migration inhibitory factor (MMIF), tumor necrosis factor (TNF), granulocytemonocyte colony stimulating factors (GMCSF) and toxic granules [8]. TGF-β1 is a profibrotic molecule and helps in remodeling of the esophagus in EoE. This may lead to esophageal luminal narrowing, stricture formation and dysmotility. Eotaxin3 is a strong chemotactic agent for esophageal eosinophilia. A single nucleotide polymorphism in the human *eotaxin-3* gene was associated with disease susceptibility. IL4 and IL13 secreted by TH2 can stimulate eotaxin3. In telomeraseimmortalized esophageal squamous cells of EoE patients, IL4 stimulated eotaxin3 secretion was blocked by PPI omeprazole and lansoprazole [9]. This may explain PPI responsiveness of esophageal eosinophilia. Twin and family studies suggest that there is not only increased prevalence of EoE in male sex but also in monozygotic twins and other family member [10]. The pathogenesis of EoE is shown in a flow diagram in **Figure 1**.

4. Pathology

The major features (**Figure 2**) include infiltration of numerous eosinophils (usually >15 per high power field) into the squamous epithelium, layering of eosinophils on the surface layer and eosinophilic microabscess formation (clusters of ≥4 eosinophils). Often necrotic squamous cells are also seen on the surface layer [11]. Minor features include chronic inflammatory infiltrate into the lamina propria with fibrosis of the lamina propria [12], hyperplasia of muscular layers and basal epithelial cells with lengthening of lamina propria papillae, and intercellular edema. One study showed plenty of IgG4containing plasma cells in the lamina propria [13]. The pathological changes are patchy in distribution, and generally affect the whole

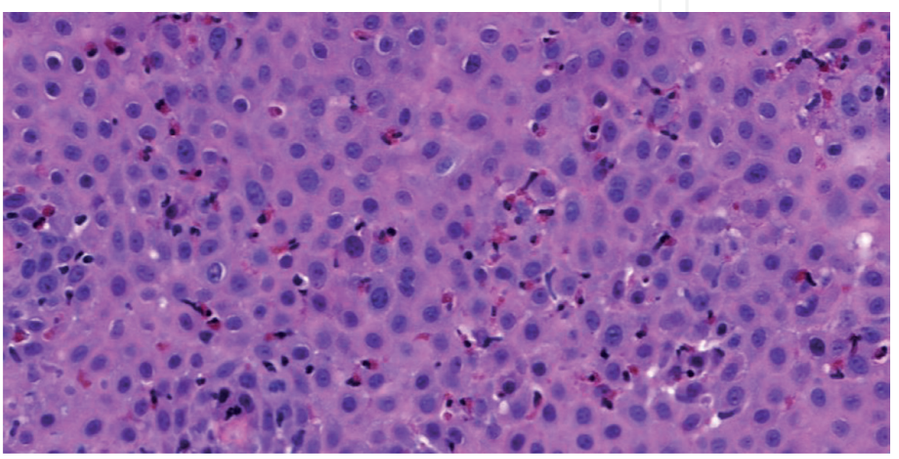

Figure 2.
HE staining showing esophageal eosinophilia.

length of the esophagus. None of the histologic findings is specific for eosinophilic esophagitis. Esophageal eosinophilia can be found in a variety of disorders including gastroesophageal reflux disease (GERD), eosinophilic gastroenteritis, hypereosinophilic syndrome, Crohn's disease, connective tissue diseases, drug hypersensitivity, parasitic and fungal infections and achalasia. In clinical practice, the real challenge comes to differentiate EoE from GERD [14]. Eosinophilic degranulation is seen more profoundly in EoE than in GERD biopsy specimen [15]. In EoE, the eosinophilic inflammation extends beyond mucosa into the submucosa and muscularis propria.

5. Clinical feature

Patients with eosinophilic esophagitis generally present with solid food dysphagia or esophageal food impaction requiring endoscopic removal of food bolus as an emergency case [16]. In one study, EoE was found in 9% of all cases of esophageal food impaction [17]. Commonly, the diagnosis is suspected after a first episode of esophageal food impaction and biopsy showing esophageal eosinophilia. Less commonly, patients present with heartburn and chest pain mimicking gastroesophageal reflux disease. One study found that gender was an important factor in the initial clinical presentation of eosinophilic esophagitis. Men presented with dysphagia and esophageal food impaction more commonly than women. Women presented with heartburn and chest pain more commonly than men [18]. Diffuse narrowing of the esophageal lumen has been seen in clinical practice as a result of chronic inflammation and fibrosis. Esophageal mucosa is friable in EoE, and as a result, esophageal mucosal tear and esophageal perforation can occur during endoscopic esophageal foreign body removal and during esophageal stricture dilation [19]. As aeroallergens play an important role in the pathogenesis, EoE is diagnosed more frequently when the environmental pollen counts (grass, trees and weeds) are high; the highest percentage of EoE occurs in the Spring and the lowest percentage in the Winter [20]. The diagnosis of EoE is not increased in the summer months [21].

6. Diagnostic tests

6.1 Laboratory (lab) tests

There is no single Lab test that can support the diagnosis of EoE. Mild peripheral eosinophilia may or may not be present. Peripheral eosinophilia, elevated serum eosinophilderived neurotoxin and eotaxin3 (CCL26) may have the potential to act as a biomarker for monitoring EoE [22].

6.2 Endoscopy

The esophageal mucosa may look normal in 7–10% of cases of EoE [23]. A variety of nonspecific features of inflammation can be seen in EoE during endoscopy. The five major endoscopic features of EoE as per EoE endoscopic reference score (EREFS) are edema, rings (**Figure 3**), exudates, furrows and strictures [24]. Edema is identified by loss of vascular markings and mucosal pallor. Transient concentric rings or trachealization may indicate esophageal longitudinal muscle contraction [25] and fixed rings may indicate fibrous stricture formation due to tissue remodeling. Exudates or white spots or white plaques may mimic candida esophagitis, histologically they are eosinophilic microabscesses. Furrows are vertical lines running parallel to the axis of the esophagus probably due to epithelial edema.

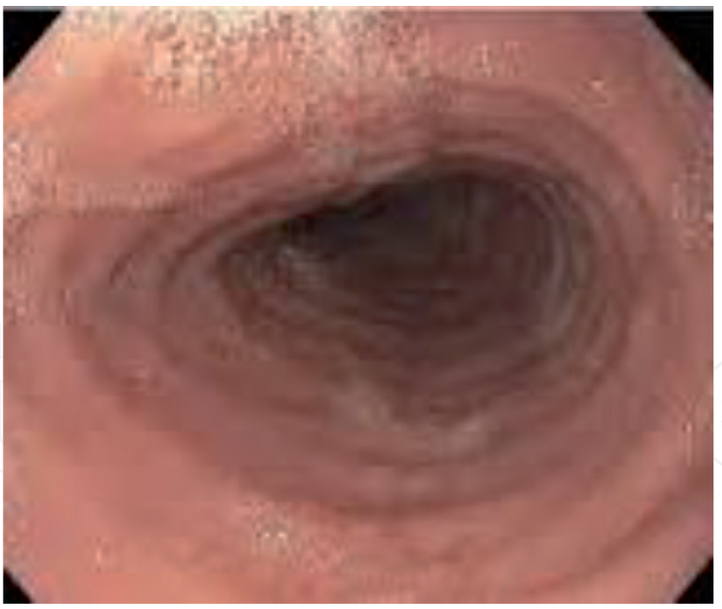

Figure 3.
Endoscopy showing multiple esophageal rings.

Chronic eosinophilic esophagitis may lead to long segment or short segment stricture. Narrowcaliber esophagus due to luminal narrowing of most of the esophagus is infrequently seen in EoE. Crepe paper esophagus occurs due to esophageal mucosal fragility and is recognized by a mucosal tear that occurs during passage of a diagnostic endoscope but neither during endoscope withdrawal nor after esophageal dilation. Although more than one of the above endoscopic findings can be seen in the same patient, none of them is specific for EoE. Recently, esophageal "pull" sign (substantial resistance and mucosal tenting during pulling of the biopsy forcep) was found to be highly specific and responsive to successful therapy in EoE patients [26].

Current recommendation is to take at least 2 to 4 biopsies from both proximal and distal halves of the esophagus (5 cm above GE junction) and also to take targeted biopsies from abnormal mucosa, *i.e.,* exudates, rings, edema, furrows and strictures. Gastric and duodenal biopsies should also be taken to evaluate eosinophilic gastroenteritis.

7. Barium swallow

Imaging studies are generally not done to diagnose EoE. Barium swallow may show normal esophagus. Sometimes featureless narrowcaliber esophagus, ringed esophagus, and isolated esophageal stricture are seen in EoE. But none is pathognomonic of EoE.

8. Esophageal manometry

Generally normal peristalsis is seen in EoE. Prolonged esophageal manometry and pHmetry showed ineffective esophageal peristalsis in children with EoE [27]. Twenty-four hours pH study would be normal in EoE unless there is coexistent GERD.

9. Echoendoscopy

Echoendoscopy may show hypoechogenesity and thickening of all the layers of the esophageal wall due to inflammation and edema [28].

10. Endotyping

In 2018, Consortium of Eosinophilic Gastrointestinal Disease Researchers analyzed endoscopic and histological features in patients with EoE using eosinophilic esophagitis diagnostic panel (EDP) which is a set of 96 informative transcripts. The EoE endoscopic reference score (EREFS), EoE histology scoring system (HSS), quantification of esophageal eosinophils and molecular features were assessed. The EDP identified clear signature of 3 distinct endotypes of EoE [29]:

1. Endotype 1 (EoEe1): It is the mild endotype. It is associated with relatively mild endoscopic (almost normal appearing esophagus), histologic and molecular changes. It is inversely associated with history of esophageal dilation. It represents 35% of all EoE patients.

2. Endotype 2 (EoEe2): It is the Inflammatory and steroid-refractory endotype. It is associated with esophagitis due to the highest expression of inflammatory cytokines. It has also the highest expression of steroid responding genes. It represents 29% of all EoE patients.

3. Endotype 3: It is the fibrostenotic and adult onset endotype. It is associated with narrow-caliber esophagus. It has the highest degree of endoscopic and histological severity and the lowest expression of epithelial differentiation genes. It represents 36% of all EoE patients.

10.1 Diagnostic criteria of EoE

1. Symptoms of esophageal dysfunction such as dysphagia, food impaction.

2. Characteristic endoscopic features: edema, rings, exudates, furrows and strictures (EREFS).

3. Esophageal eosinophilia i.e. > 15 eosinophils per high power field.

4. Exclusion of other causes of esophageal eosinophilia.

11. Management

Firm diagnosis of EoE is essential before offering any treatment. Symptomatic esophageal eosinophilia is now considered as EoE when other secondary/non-EoE causes are excluded [30]. Few years ago, the term proton pump inhibitor responsive esophageal eosinophilia (PPI REE) was used [31] but EoE and PPIREE are indistinguishable clinically, endoscopically and pathologically. The term PPI-REE is no longer used at the present time. The main aim of treatment of EoE is not only clinical improvement but also histological improvement to prevent development of esophageal stricture. In 2020, the American Gastroenterology Association (AGA) and the Joint Task Force on Allergy-Immunology Practice Parameters (JTF) recommended certain guidelines on the management of EoE [32]. Currently, drugs, diet and dilation are the three main modalities of treatment of EoE.

12. Drugs

12.1 PPI

PPI is now used as the first-line treatment of EoE. In adults patients treated with PPI, symptomatic improvement can range from 25–80% and histological remission from 33–61% [33]. As mentioned before, PPI can block IL-4 stimulated eotaxin-3 secretion and thus can inhibit eosinophil recruitment from blood into the esophageal tissue [34]. Significant improvement of dysphagia can occur in few days' time. PPI can also be used as an adjunctive therapy when patients with EoE require esophageal dilation. Richter et al. found that esophageal eosinophilia was decreased in patients who received combination of PPI and esophageal dilation but not in patients who had esophageal dilation alone [35]. Finally, PPI can also restore the esophageal mucosal barrier function in patients with EoE and thus can inhibit the entry of aeroallergens into the esophageal mucosa [36]. It is author's opinion that in endotype 1, full dose of PPI once a day or low dose PPI twice a day should be initiated. Patients should be evaluated for symptomatic/clinical response after 4 weeks. At that time, there will be 2 groups:

1. Non-responders or inadequate clinical responders: dose of the PPI should be doubled and the patient should be evaluated again after 4 weeks. If there is no improvement of clinical response after 4 weeks, alternate therapy should be considered.

2. Responders or adequate clinical responders: same dose of PPI should be continued for another 4 weeks. Then the dose of PPI should be lowered to maintain controlling patient's symptoms.

A recent study found that in endotype 2, continuation of PPI therapy for at least 12 weeks had greater chance of inducing remission of EoE whereas in endotype 3, there was less responsiveness to PPI therapy both in the beginning and in the long run [37].

12.2 Topical glucocorticosteroids

Have become the second line medications for the treatment of EoE. Fluticasone metered dose inhaler 880 microgram puffed directly into the mouth without breathing and then dry swallowed twice a day for 6 to 8 weeks has been found to be effective in reducing symptoms and esophageal eosinophilia in 50 to 80% of cases [38, 39]. Patients are advised not to take any food or drink or rinse their mouth for half an hour to prevent the medication from washing off the esophageal mucosa. The maximal anti-inflammatory effect is found in proximal esophagus. Oral viscous budesonide (OVB) 1 mg twice a day also decreases dysphagia and esophageal eosinophilia. OVB is easy to swallow, more mucoadherent and is made by mixing aqueous solution of budesonide (1 mg/2 mL) with the sugar substitute sucralose (5 g), chocolate syrup or honey [40]. Both forms of topical corticosteroids are more effective in histologic improvement than symptomatic improvement. Only 1% of the topical steroid is absorbed, so systemic side effects are extremely rare although oral and esophageal candidiasis can occur in up to one third of the time and herpes simplex esophagitis have been reported rarely.

Topical steroid is generally given for 8 weeks. If that fails, prolonged or higher doses of topical steroids or systemic steroids or dietary treatment or esophageal dilation should be tried to get symptomatic improvement. The AGA/JTF suggests

continuation of topical glucocortisteroids as maintenance therapy in patients with EoE in remission after short-term use of topical glucocoticosteroids.

13. Diet

Dietary therapy is very effective in the management of EoE. It can be used as an initial therapy or when other modalities of treatments fail. Dietary therapy depends on the resources available and can be expensive. As the dietary food allergen is removed, dietary therapy is very effective in inducing and maintaining clinicopathological remission. The three ways of dietary modification include:

1. Elemental diet: Amino acid based formula to remove food allergens. This therapy when given for a minimum of 6 weeks did both symptomatic and histologic improvement (95% and 98% respectively) in EoE patients [41]. But the amino acid formula is expensive and unpalatable which affect patients' quality of life, especially in children.

2. Sixfood group elimination diet (SFGED): The most common food allergens in EoE include milk, egg, wheat, soy, peanuts/tree nuts and sea food (fish/shellfish). Significant clinical and histological (74%) improvement occurred in EoE patients (children) when they were on this SFGED [42]. Another study showed fourfood group elimination diet (FFGED) which excludes milk, egg, wheat and legumes, when given for 6 weeks, clinicopathological remission occurred in 54% of adult EoE patient [43], and

3. Targeted or tailored elimination diet: This therapy is guided by detection of food allergens by skin prick/patch tests and blood tests. These tests can be not only time consuming but also can give false positive and false negative results. This therapy is offered as per the preference of the patient. Sixty-eight percent of EoE patients had symptomatic improvement on targeted therapy [44]. A dietitian interested in food allergies and EoE should be consulted. An Allergist should also be involved to find out the allergens triggering EoE. Food challenge by introducing one food or food group every 4 to 6 weeks should be offered. If the patient is allergic to food, there will be recurrence of symptoms and esophageal eosinophilia [45]. The AGA/JTF suggests using elemental diet or SFGED or testing based elimination diet over no treatment.

14. Systemic steroids

Oral methylprednisolone induced marked clinical and histological improvement in pediatric EoE patients [46]. Because of systemic side effects, this therapy is reserved when other therapeutic interventions fail. Steroids work by reducing the synthesis of eota xin3, IL5 and GMCSF, and inducing the apoptosis of eosinophils. But recurrence of the EoE occurs after withdrawal of the steroids. The AGA/JTF suggests topical glucocorticosteroids rather than systemic steroids should be used in patients with EoE.

15. Immunomodulators

Azathiopurine and 6mercaptopurine induced and maintained clinical and histological remission in steroid dependent EoE patients in a case series [47]. They are not currently recommended for routine clinical use in EoE.

16. Mast cell stabilizers

In a small case series, Cromolyn sodium failed to show any clinical or histologic improvement in EoE patients [48].

17. Leukotriene inhibitors

Montelukast is an eosinophil stabilizing agent. It improved clinical symptoms in EoE but there was no histological improvement [49].

17.1 IL-4 inhibitor

Dupilumab is an interleukin-4 receptor antagonist/monoclonal antibody. It has been found to be effective in improving dysphagia and esophageal eosinophilia (intraepithelial eosinophil count of ≤6 eosinophils per high-power field) in a double blind, placebo-controlled, pivotal phase 3 trial (Part A) that evaluated its efficacy in 81 patients aged ≥12 years with EoE. Dupilumab was granted Breakthrough Therapy designation by the FDA (Food and Drug Administration, USA) in September, 2020 for the treatment of the patients aged ≥12 years with EoE [50]. This designation would allow expedited review of dupilumab for the FDA approval.

17.2 IL-13 inhibitor

RPC4046 (a humanized monoclonal antibody against IL13) was found to improve dysphagia, and reduce histologic and endoscopic features compared with placebo in a phase II trial. The medication was also found to be safe and well tolerated [51].

17.3 IL-5 inhibitor

AntiIL5 antibody has been studied in both pediatric and adult patients with EoE. Mepolizumab significantly reduced esophageal eosinophilia but there was minimum symptomatic improvement [52]. Reslizumab also improved esophageal eosinophilia in EoE but there was no difference in clinical improvement in comparison to placebo [53, 54].

17.4 Macrophage migration inhibitory factor (MIF)

Macrophage migration inhibitory factor (MIF) is overexpressed in the esophageal mucosa of EoE patients. Recently, in the mice model of EoE, early administration a drug that blocked the action of MIF prevented eosinophilic infiltration in the esophagus. This study can lead to a novel therapy in future if MIF effect can be blocked in EoE patients [55].

The medications investigated for the treatment of EoE can be grouped as follows:

- Medications with proven effectiveness: PPI, topical glucocorticoids, systemic steroids. Immunomodulators.
- Medications under development: IL-4 inhibitor, IL-13 inhibitor, MIF.
- Medications with proven ineffectiveness: mast cell stabilizers, leukotriene inhibitors, IL-5 inhibitors.

18. Endoscopic treatment

Esophageal dilation has definitive role in the management of EoE. Dilation is not indicated in patients with normal caliber esophagus and signs of inflammation during endoscopy [56]. It is very effective in symptomatic esophageal stricture (esophageal diameter < 10 mm), long segment narrowing and narrow caliber esophagus. This modality of treatment improves dysphagia and quality of life but does not reduce esophageal eosinophilia [57]. Either hydrostatic balloon dilation or wire guided bougie dilation can be done. Esophageal diameter should be 15 to 18 mm to relieve dysphagia. Patients may need multiple sessions to achieve this. There is an increased risk of mucosal tear causing postdilation chest pain for several days [58]. Although initially thought that EoE patients carry higher risk of perforation after esophageal dilation, systematic review did not show any higher risk of perforation (0.1%) in this group of patients [59].

18.1 Endoscopic surveillance

Currently there is no guideline when surveillance endoscopy should be done in EoE patients who have achieved remission. In clinical practice, endoscopic and histologic assessment should be done 6 to 8 weeks after initiation or change of treatment to evaluate the efficacy of the treatment. When the disease is under remission, less frequent assessment/surveillance is done on a yearly basis or less frequently depending on the clinical scenario and the clinician.

18.2 Prognosis

As mentioned earlier, EoE is a chronic inflammatory disease of the esophagus. The inflammation leads to remodeling, fibrosis and stricture. Fortunately, no case of esophageal malignancy has been reported in EoE. Patients are generally diagnosed after several years of their symptoms. Although symptomatic improvement occurs after treatment, recurrence is common after discontinuation of treatment. So maintenance therapy is needed to prevent recurrences. At the present time there is no head to head study to suggest the best maintenance treatment. Continuation of PPI, swallowed glucocorticosteroid and/or dietary therapy should be done in all EoE patients particularly in those with history of food impaction, dysphagia, esophageal stricture, and in those with rapid symptomatic and histologic relapse following initial treatment.

19. Summary

EoE has become a common clinical entity in patients with dysphagia and esophageal food impaction. Although the disease is more common in young male patients with allergic disorders, any person can get affected. High degree of suspicion is essential to diagnose this disease. So multiple proximal and distal esophageal biopsies should be taken in EoE suggestive mucosa (EREFS) and even in normal looking mucosa. Other causes of esophageal eosinophilia particularly GERD, eosinophilic gastroenteritis and hypereosinophilic syndrome should be considered. The morbidity can be managed and long-term complications can be prevented by a multidisciplinary team which includes gastroenterologists, pathologists, allergists and dietitians. Patients with EoE should be given PPI therapy or topical glucocorticosteroids for 8 to 12 wk. If there is no clinicoopathological improvement i.e., in treatment-resistant cases, esophageal dilation should be offered [60]. Esophageal

dilation in combination with PPI therapy or topical glucocorticosteroid therapy should be offered to patients with esophageal strictures and narrow caliber lumen. Lowest effective dose of PPI therapy or topical glucocorticosteroid should be continued to all EoE patients as maintenance therapy to reduce progression of the disease and relapse. Patients with EoE should be referred to the dietitians interested in food allergies and EoE patients. The AGA/JTF recommends using immunomodulators, IL-4 inhibitor or IL-13 inhibitor *only* in the context of clinical trial.

Conflict of interest

None.

Author contribution

Monjur Ahmed, MD, FRCP solely contributed to this work.

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