Eosinophilic esophagitis
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ABSTRACT

Eosinophilic esophagitis (EoE) is a clinico-pathological entity characterised by symptoms of esophageal dysfunction and eosinophilia on esophageal mucosal biopsies in the absence of other causes of esophageal eosinophilia. It is a chronic inflammatory condition of esophagus often characterized by refractory reflux symptoms in children and dysphagia in adults. It occurs as a result of Th2 inflammatory response to environmental triggers (food antigens) in genetically predisposed individuals. The diagnostic criteria include symptoms of esophageal dysfunction, esophageal eosinophilia (> 15/hpf), and a PPI trial (persistent eosinophilia after 8 weeks of PPI). Mainstay of treatment at present is topical steroids and dietary therapy. Maintenance treatment should be considered to prevent long term complications.

KEYWORDS: Eosinophilic esophagitis, gastroesophageal reflux disease, dysphagia, chronic inflammation

Introduction

Eosinophilic esophagitis (EoE) is a clinico-pathological entity characterised by symptoms of esophageal dysfunction and eosinophilia on esophageal mucosal biopsies in the absence of other causes of esophageal eosinophilia. Landres et al first described EoE in 1978. Since then, there were very few reports on this disease till late 1990s, when this condition started becoming increasingly recognised. It is a chronic inflammatory condition of esophagus often characterized by refractory reflux symptoms in children and dysphagia in adults. The definition, diagnostic and management approach has evolved considerably over the last two decades and the understanding about this disease is expected to improve further in the future. This review will try to provide latest information on the diagnostic and management approach to EoE.

Pathogenesis

Eosinophilic esophagitis is a chronic inflammatory condition of the esophagus which is believed to occur as a result of Th2 inflammatory response to environmental triggers (food antigens) in genetically predisposed individuals (Figure 1). The cytokines responsible for the Th2 inflammatory response include Interleukin (IL)-4, IL-5 and IL-13. These cytokines stimulate the production and upregulation of Eotaxin-3 (potent...
eosinophilic chemokine) in the esophageal mucosa. Eotaxin-3 in turn causes recruitment of eosinophils to the esophageal mucosa. These eosinophils secrete pro-inflammatory and fibrogenetic cytokines which cause tissue damage, recruit additional inflammatory cells such as mast cells and fibroblasts and cause tissue remodelling. EoE represents a varied manifestation of atopy. This is suggested by the fact that there is a significant allergic predisposition as concurrent allergic rhinitis, eczema or asthma seen in a majority of EoE patients. Chronic esophageal inflammation leads to esophageal tissue remodelling and fibrosis which results in symptoms of dysphagia. TGF-β1 plays a pivotal role as a profibrotic factor in causing esophageal smooth muscle contraction and fibrosis.

**Genetics of EoE**

EoE occurs in multiple family members, in a non Mendelian manner suggesting a polygenic complex pattern of inheritance. EoE has been reported to have a racial as well as gender bias. Multiple epidemiological studies have shown predominance of European white ancestry and male gender amongst EoE patients. Recent reports have suggested role of genetic polymorphisms in the pathogenesis of EoE. A recent study showed that approximately 10% parents of EoE children had history of esophageal strictures and 8% had eosinophilic infiltrates on esophageal biopsies. It has also been shown that EoE is associated with a sibling risk ratio of 80, which means that there 80 fold risk of developing EoE in a sibling of patient with EoE. Genome wide association studies have identified 6 loci which are associated with EoE (Table 1). Eotaxin-3 (CCL26) followed by Thymic stromal lymphoprotein (TSLP) located on chromosome 5q22 were the first susceptibility genes associated with EoE. Other genetic loci include two loci which have previously been associated with other atopic and autoimmune diseases (c11orf30 and STAT6) and two EoE specific loci; ANKRD27 (regulates trafficking of melanogenic enzymes to epidermal melanocytes) and CAPN14 which encodes a calcium binding protease (calpain) that is specific to esophagus.

**Epidemiology**

EoE is increasingly being seen and recognized possibly because of increasing incidence as well as awareness of the disease. It has been predominantly reported from Western industrialized countries with high socioeconomic development. It has been shown that incidence of EoE in children may vary from 0.7 to 10/100,000 and prevalence from 0.2 to 43/100,000 depending on the geographic location. In adult cohorts, the prevalence rate of 52/100,000 has been reported on the basis of a survey done in USA. It is a disease of middle age adult males as the average age of presentation is 30 to 50 years with 60-80% of all cases diagnosed being males. In a recent study from our centre (unpublished), the prevalence of EoE in

| Gene     | Chromosome | Function                                                                 |
|----------|------------|--------------------------------------------------------------------------|
| CCL26    | 7q11.2     | Eosinophil chemoattractant, recruits eosinophils to esophageal mucosa     |
| TSLP     | 5q22       | Encodes IL-7 like cytokine which regulates dendritic cell mediated inflammatory Th2 responses |
| C11orf30 | 11q13.5    | Encodes EMSY, a transcriptional regulator which is amplified in human mammary adenocarcinomas |
| STAT6    | 12q13.3    | Plays a key role in IL-4 pathway                                          |
| ANKRD27  | 19q13.11   | Regulates trafficking of melanogenic enzymes to epidermal melanocytes     |
| CAPN14   | 2p23.1     | Encodes a calcium binding protease (calpain) that is specific to esophagus |

Table 1: Genetic polymorphisms associated with Eosinophilic esophagitis
patients with GERD was 3.2%. Six out of 192 patients with GERD were diagnosed with EoE. Non response to PPI and history of allergy were predictive of diagnosis of EoE.

**Clinical features**

Symptoms depend upon the age of the patient. Children usually present with feeding difficulties, failure to thrive, abdominal pain, chest pain, nausea, vomiting, and regurgitation. Dysphagia is the most common symptom in adolescents and adults, seen in 25 – 100% patients. Other features include history of sudden onset food impaction, chest pain and heartburn. However the symptoms of EoE are very non-specific and no symptom in isolation points towards the diagnosis of EoE. Approximately 60 – 80% children and fewer adults have a history of associated allergic diseases such as asthma, atopic dermatitis, atopic rhinitis and food allergies. EoE should always be considered as a possibility in the clinical scenario of heartburn refractory to anti reflux therapy. However, a distinction should be made between proton pump responsive esophageal eosinophilia. Peripheral eosinophilia is seen in 5-50% of patients and approximately three fourths of the patients have elevated total serum IgE levels.

**Endoscopic features**

Similar to clinical features, the endoscopic features are also non-specific and none of the features is pathognomonic to EoE. The important features include concentric rings (corrugations), linear furrows, loss of vascular pattern due to mucosal edema, exudates or white plaques, narrow calibre esophagus, strictures and crepe paper esophagus (fragile esophageal mucosa which lacerates due to passage of endoscope). The findings can occur together or in isolation. Approximately 10% patients can have normal endoscopic findings, and diagnosis can be missed if biopsies are not taken. There is also a moderate degree of inter-observer and intra-observer variability in the interpretation of endoscopic findings as per two recent studies. It is for this reason that biopsies should be obtained in all suspected cases of EoE even if the endoscopy is normal. Since the eosinophilic infiltrate in the esophagus is patchy, at least 4 biopsies should be obtained both from both proximal and distal esophagus for optimal yield. A recent study showed that esophageal biopsy “pull” sign (resistance felt when pulling biopsy forceps to obtain tissue) was highly specific and treatment responsive endoscopic finding in EoE.

**Histological features (Figure 2)**

Eosinophils are normal constituents of gastrointestinal tract except the esophagus. The pathological characteristic of EoE is eosinophilic infiltrate in the esophageal epithelium, with greater than 15 eosinophils/hpf in at least one high power field suggesting the diagnosis of EoE. However like endoscopic features, the pathology is also non-specific and not pathognomonic for EoE and should be interpreted in association with clinical and endoscopic features. Other histologic features include eosinophilic microabscesses (clusters of > 4 eosinophils), superficial layering of eosinophils, extracellular eosinophilic granules (comprising of eosinophil peroxidase, major basic protein and eosinophilic derived neurotoxin), rete peg elongation, basal cell hyperplasia, and lamina propria fibrosis.
Diagnosis of eosinophilic esophagitis

Diagnosis of EoE is made on the basis of clinical, endoscopic and histological features after exclusion of other etiologies. The closest differential of EoE includes two clinical entities: gastroesophageal reflux disease (GERD) and proton pump inhibitor responsive esophageal eosinophilia (PPI-REE). Other systemic conditions which can be associated with esophageal eosinophilia include other eosinophilic gastrointestinal disorders, celiac disease, inflammatory bowel disease, hyper-eosinophilic syndrome, drug hypersensitivity, vasculitis and connective tissue disorders. These disorders should be excluded before entertaining the diagnosis of EoE.

There are 3 diagnostic criteria for the diagnosis of EoE (Table 2): a) symptoms of esophageal dysfunction, b) eosinophilic infiltrate (>15/hpf) of esophageal biopsy, and c) exclusion of other disorders, primarily GERD and PPI-REE after a PPI trial which consists of 8 week course of 20 – 40 mg twice daily of any available PPI. Persistence of eosinophilic infiltrate after PPI trial excludes GERD and PPI-REE and diagnosis of EoE is confirmed. Approximately 1/3rd patients with symptoms of esophageal dysfunction and eosinophilic infiltrate respond clinically and histologically to PPI.

Role of non-invasive modalities in differentiating EoE from GERD and monitoring treatment

Several groups have derived prediction tools and models to differentiate EoE from GERD and predict EoE without biopsy. Aceves et al in a study of EoE and GERD patients showed that dysphagia, anorexia/ early satiety were more common in EoE. In another retrospective study it was shown that history of food impaction, PPI refractory heartburn and peripheral eosinophilia were predictive of EoE with a sensitivity of 91% and specificity of 100%. Another group generated a predictive model in 163 paediatric and adult EoE and equal number of GERD cases. They showed that a set of 6 characteristics: male sex, history of dysphagia, heartburn, food impaction, and furrows and plaques on endoscopy were able to differentiate EoE from GERD with an area under the curve (AUC) of 0.86. Dellon et al in a recent study developed a predictive model (based on clinical and endoscopic features) which could recognize patients (with symptoms of esophageal dysfunction) as having a very high possibility of EoE as well as those in whom there in very low possibility of EoE. This model included eight measures: age, sex, history of dysphagia and food allergy, presence of endoscopic rings, furrows, plaques and lack of hiatus hernia. As this model had a very high specificity and negative predictive value it could accurately identify patients unlikely to have EoE and could avoid biopsy.

A recent study examined the role of non-invasive biomarkers to monitor treatment response in EoE. In patients randomized to placebo and budesonide, absolute eosinophil count (AEC), serum levels of CCL-17, CCL-18, CCL-26, eosinophilic cationic protein (ECP) and mast cell tryptase (MCT) were determined and correlated with symptoms, endoscopic scores and esophageal eosinophilic density. All of the above studied markers decreased significantly in the budesonide arm and correlated with decline in esophageal eosinophils. Of these markers AEC was shown to be the most valuable serum marker.
Treatment of eosinophilic esophagitis

Therapeutic Indications

The established indications to treat EoE are: presence of solid food dysphagia, to prevent food impaction and prevention of esophageal damage caused by tissue remodelling. The non established indication for treatment is prevention of herpes simplex (HSV-1) esophagitis. The reason being that acute esophageal inflammation may be risk factor in immunocompetent individuals for HSV1 infection.

Therapeutic goals

The primary goals of treating eosinophilic esophagitis include symptom improvement, histological improvement (elimination of esophageal eosinophilia), maintenance of symptomatic relief, minimization of adverse events and improvement in quality of life. It is still debatable if the therapeutic endpoint should be symptomatic improvement or histological remission.

The three primary treatment modalities are drugs, dietary therapy and endoscopic dilatation in selected cases.

Pharmacological treatment

The mainstay of pharmacological treatment of EoE are topical corticosteroids, which include inhaled fluticasone, nebulizer solution of budesonide and oral viscous budesonide. These preparations were primarily designed for asthma treatment (inhaled or nebulisation solutions), but instead of inhalation they are swallowed orally. When swallowed these preparations coat the esophageal mucosa and act locally. The primary treatment endpoints have varied in various trials including symptomatic and histological improvement. These trials also show that there is little correlation between symptomatic and histological resolution. Histological end points have also varied between various trials.

Fluticasone

Fluticasone is used in two divided doses (Table 3) as multidose inhaler which is swallowed orally. The medication should be administered directly into the mouth without the spacer, and without inhaling during actuation. The patient should not eat or drink for 30 minutes after swallowing the drug. All the three RCTS of fluticasone vs placebo (Table 4) showed significant improvement in esophageal eosinophilia. However the definition and degree of symptomatic improvement was different in all the three trials. The first trial by Konikoff et al in children showed improvement in vomiting in the treatment arm. The other two trials did not show any significant improvement in patient symptoms. Fluticasone has also been compared with oral prednisolone and oral esomeprazole in two RCTs. There was > 90% symptomatic and histologic improvement in both the fluticasone and prednisolone arms. However more patients had complete histological remission with prednisone as compared with fluticasone (81% vs 50%). There was no difference in histologic response when fluticasone was compared with esomeprazole, however symptoms improved significantly with fluticasone. Fluticasone has also been used in nasal drop formulation, and was shown to be effective in a case series.

Table 3: Doses of topical steroids for treatment of Eosinophilic esophagitis

| Drug        | Dose according to age Group |
|-------------|-----------------------------|
| Fluticasone | 88 – 440 mcg/day* Children 880 – 1760 mcg/day* Adults |
| Budesonide  | 1 mg/day adults 2 mg/day* |

*Used typically in two divided doses

Table 4: Summary of RCTs on topical steroids for treatment of Eosinophilic esophagitis

| Author/year | Treatment | Comparator | Patients | Histologic outcome (%) | Symptom improvement |
|-------------|-----------|------------|----------|------------------------|---------------------|
| Konikoff 2006 | Fluticasone 21 | Placebo 15 | Children | 50 9 | 67% 27% |
| Schaefer 2008 | Fluticasone 40 | Oral prednisone 40 | Children | 94 94 | 97% 100% |
| Straumann 2010 | Budesonide 18 | Placebo 18 | Adults 72 11 | Present Absent |
| Peterson 2010 | Fluticasone 15 | Esomeprazole 15 | Adults | 15 33 | 50% 25% |
| Dohil 2010 | Viscous budesonide 15 | Placebo 9 | Children 87 0 | Present Absent |
| Gupta 2011 | Budesonide 53 | Placebo 18 | Children 77 0 | Present Present |
| Alexander 2012 | Fluticasone 21 | Placebo 15 | Adults 68 0 | Present Present |
| Dellon 2012 | Viscous budesonide 13 | Inhaled bud. 12 | Adults 64 27 | 15 10 |
| Butz 2014 | Fluticasone 28 | Placebo 14 | Adults & children 65 0 | Present Absent |
**Budesonide**

There are 4 RCTs on different forms of budesonide,84-86 three have compared it with placebo and fourth one compared two different forms of budesonide (inhaled vs oral viscous).87 All placebo controlled trials showed significant histological improvement. However, symptomatic improvement as compared to placebo was seen in two trials only. Oral viscous budesonide (OVB) was developed by mixing budesonide aqueous solution with sucralose to form a sweet and easy to swallow paste. A study which compared OVB to inhaled solution showed greater histologic improvement and higher mucosal medication contact as measured by scintigraphy with OVB. However there was no difference in the degree of symptomatic improvement in both the groups.

In addition to sucralose, budesonide has also been used with other forms of thickeners including corn starch, powdered sugar, honey and neocate nutra.88 Budesonide has also been used as oral budesonide suspension (OBS), and in an RCT it was shown to be effective than placebo in histological and symptomatic improvement.86

A recent study which compared inhaled fluticasone and budesonide in EoE found equal efficacy for both topical steroid preparations in terms of histological and symptomatic response.89

**Other topical steroid preparations**

Other topical steroids which have been used for this indication include ciclesonide (used as multi-dose inhalers)90 and mometasone (used as nasal preparation).91

Two recent systemic review and meta-analysis concluded that topical steroids were effective for histological remission; however the efficacy remains undetermined for symptomatic improvement and endoscopic remission.92,93

There are no major side effects with topical steroids. The risk of adrenal suppression with topical steroids remains controversial. There are recent reports both in favour of94,95 and against adrenal suppression96 with the use of inhaled steroids in EoE. The rates of oral and esophageal candidiasis has also been low varying from 0 – 30% in various reports with most the cases being asymptomatic and detected incidentally.

**Other pharmacological agents**

Oral steroids: The RCT that compared fluticasone and prednisolone showed similar results.81 However prednisolone was associated with greater degree of adverse events. Oral steroids are recommended when topical preparations are ineffective or when rapid improvement in symptoms is required.

Leukotriene antagonists: There are no controlled trials for these agents (monteleukast) in EoE. Case series in both children and adults did not show promising results.97-98 These agents are therefore not recommended for treatment of EoE.

Mast cell stabilizers: Mast cells play a key role in pathogenesis of EoE. However based on their inefficacy in case series, they are not recommended for treating EoE.99

Immunomodulators (Azothioprine/ 6-mercaptopurine (MP)): Three adults with steroid refractory disease were successfully treated with azathioprine and remained in remission till the treatment was continued. However the data on use of these agents is still scarce,100 and they are not recommended as first line maintenance agents for treatment of EoE.

Biologics: Interleukin-5 is a key player in the pathogenesis of EoE. Antibodies to IL-5, mepolizumab and reslizumab102 have been studied for the treatment of EoE.102-104 There have been case series and RCTs on the use of these antibodies and have demonstrated modest decline in esophageal eosinophilia, with no significant improvement in symptoms. Another class of antibodies against IgE (omalizumab) also did not show any histological or symptomatic improvement.105 These agents are therefore not recommended for use in EoE. A small case series of anti TNF antibodies in EoE also did not show any benefit.106

**Dietary therapy**

Food allergens are the most important environmental factors that play a significant role in the pathogenesis of EoE.107 Therefore avoidance of food antigens would be an important therapeutic strategy for EoE. There are three strategies for dietary approach in EoE; elemental diet, targeted elimination diet (after allergic testing) and six food elimination diet (SFED).

Elemental diet comprises of amino acids, basic carbohydrates and medium chain tri-glycerides. It therefore eliminates all possible antigens from the diet. Several case series from children have shown excellent symptomatic as well as histological response.108-109 However studies in adults did not replicate the results in children, probably because of low compliance in adults.110 Although it is associated with excellent outcomes, elemental diet is unpalatable, and is associated with
a very poor compliance especially in adults. It is also expensive
and may require enteral feeding tube for administration.

Because of problems associated with elemental diet a dietary
approach was developed which eliminated six food items that
were most strongly associated with food allergy. These
include milk, egg, wheat, soy, sea food and nuts. Studies in
both children and adults have shown good symptomatic as
well as histological response, comparable with elimination diet.
Reintroduction with these food items showed that wheat and
milk were the most common food triggers.

The third dietary approach consists of allergic testing to
eliminate possible food allergens. The possible strategies
for allergic testing include skin prick and patch testing. However
the best approach for allergic testing is still debatable. The
response rates with this approach have been modest
ranging from 50 – 70% in children and bit lower in adults.

A recent meta-analysis which included 1317 patients (1128
children, 189 adults) from 33 studies compared histological
response will all the above mentioned strategies. Elemental
diet was the most effective (90.8%) followed by SFED (72.1%).
Targeted dietary approach was the least effective (45.5%).
There was no significant difference in the efficacy of dietary
interventions between adults and children (67.2% vs 63.3%).

Maintenance therapy for EoE

The duration of treatment in various trials of pharmacological
and dietary therapy has varied from 2 weeks to 16 weeks. However,
very few trials have assessed the role of these agents
in maintenance of remission. Since EoE is a chronic inflammatory
condition relapse is expected after initial induction of remission
once the treatment is stopped. Therefore, to prevent remodelling
of esophageal mucosa and long term complications remission
once achieved should be maintained. In a study which randomized
patients to budesonide (0.5 mg/day) vs placebo
after achieving remission, there was universal histological
recurrence in the placebo group as compared to 50% is the
budesonide group. Symptomatic recurrence was also less in
budesonide arm as compared to placebo (36% vs 64%). In
another study inhaled fluticasone was used in a high dose
(1760 mcg/day) for attaining remission. After 3 months of
therapy, patients who achieved complete remission (CR) were
started on half of the initial dose (880 mcg/day). Sixty five
percent patients achieved CR during induction. Of these 65%
patients, 73% remained in remission on low dose fluticasone.
Regarding the role of dietary therapy in maintenance a
prospective study was conducted on six food elimination diet
(SFED) in 67 adults with EoE. These patients were induced
with SFED for 6 weeks and subsequent re-introduction with
each of the single food item was done followed by endoscopies
and biopsies. Food item was considered as a trigger if
esophageal eosinophilia (>15/hpf) reappeared on follow-up
biopsies. Patients who continued to avoid the offending food
item remained in clinical and histological remission for up to
three years. However the duration of maintenance therapy still
remains unclear and should be individualized.

In patients refractory to topical steroids and dietary therapy,
induction can be achieved with oral steroids and remission
can be maintained with immunomodulators as was shown in a
small case series.

Role of endoscopic dilatation

Endoscopic dilatation is indicated in patients with esophageal
strictures or with narrow calibre esophagus, who have
significant symptoms of dysphagia after adequate
pharmacological and dietary therapy. Esophageal dilatation
improves symptoms of dysphagia effectively with one study
reporting 81% symptomatic response at 3 months post dilatation.
However, esophageal dilatation should be deferred
during the first endoscopy, before any therapy has been started.
This is based on a recent RCT in which 31 patients were
randomized to dilatation vs no dilatation. Seventeen patients
underwent esophageal dilatation before medical therapy and
14 patients were kept on medical therapy alone. There was no
additional advantage of esophageal dilatation in improvement
of dysphagia.

Initial reports of dilatation in patients with EoE, raised many
alarms as it was associated with high rates of complications
including post dilatation chest pain, esophageal tears, and
esophageal perforation which was seen in as high as 8%
dilatations. However recent studies including two systematic
reviews have negated this concern and cumulative data on
over 1000 dilatations has revealed a perforation rate of 0.3%
only, which is similar to the rates associated with dilatation
for other indications. Secondly all these perforations were
managed conservatively and none required operative
interventions. Therefore currently dilatation is an accepted
therapeutic modality for EoE if performed cautiously.

There is no definite consensus over the technique of
dilatation (bougie vs balloon). Both techniques have their own
advantages and limitations and the preferred technique depends
upon the type of stricture and individual preference.

**Investigational agents**

As new information on the pathogenesis of EoE is being discovered several new treatment modalities are being discovered.

Anti IL-13: Interleukin 13 is a Th2 cytokine that plays an important role in the pathogenesis of EoE, and has shown to be up regulated in the esophageal mucosa of EoE patients. In a study of 25 patients who were randomized to anti IL-13 antibody (QAX576) and placebo, there was histological and symptomatic, but statistically non-significant benefit with anti-IL13 antibody. Further data is needed before this agent can be used in treatment of EoE.

CRTH2 antagonist: CRTH2 (Chemoattractant receptor homologous molecule expressed on TH2 cells) is a prostaglandin D2 receptor, implicated in various allergic diseases. CRTH2 antagonist OC000459 was studied in a RCT which randomized 26 patients to OC000459 and placebo. There was a statistically significant reduction in esophageal eosinophilia with OC000459 as compared to placebo, however there was no difference in the degree of symptomatic improvement between the two groups.

**Conclusion**

Eosinophilic esophagitis is a chronic inflammatory disorder which is mediated by a Th2 inflammatory response in response to environmental/food allergens in individuals with genetic background. The diagnosis requires high index of suspicion, especially in young and middle age male patients with dysphagia, patients with PPI refractory heartburn, presence typical endoscopic features and eosinophilia on biopsy. The diagnostic criteria include symptoms of esophageal dysfunction, esophageal eosinophilia (> 15/hpf), and a PPI trial (persistent eosinophilia after 8 weeks of PPI). Mainstay of treatment at present is topical steroids and dietary therapy. Maintenance treatment should be considered to prevent long term complications. Esophageal dilatation should only be considered in patients who are symptomatic despite inhaled steroid/ dietary therapy. There is a lot of progress in the understanding of pathogenesis of EoE which is opening up new dimensions in the diagnosis (including role of non-invasive markers) and treatment of these disease entity. There has been a considerable progress in identifying genetic polymorphism associated with EoE which in future could lead to development of targeted therapies for EoE.

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