Eosinophilic esophagitis – Associations

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Abstract:
Eosinophilic esophagitis (EoE), a chronic immune mediated disease, is associated with various immune and non-immune mediated conditions that include allergic diseases, atopic diseases, inflammatory bowel diseases, schatzki ring, celiac disease, esophageal atresia, herpetic esophagitis, connective tissue diseases, cystic fibrosis, helicobacter pylori infection and Barrett’s esophagus. Scientific publications investigating association of these diseases with EoE were reviewed from Internet databases and summarized to have an overview of the association of these diseases with EoE. Possible pathogenesis that are associated with these diseases and EoE were looked for as insight into the pathogenesis leading to the associations might help in early diagnosis and treatment of the associated diseases.

Keywords: allergic diseases, eosinophilic esophagitis and esophagitis

Introduction
Eosinophilic esophagitis is a chronic immune mediated disease commonly triggered by food or aeroallergens resulting in a pathologically remodeled esophagus with abnormal biomechanics and symptoms of dysphagia and food impaction. EoE had been found to share features with atopic diseases like asthma and atopic dermatitis(1). Concomitant occurrence of EoE and celiac disease have been reported and discussed for possible association since 2007(2). EoE shares the common pathophysiological mechanism of immune system disruption with other gastrointestinal diseases like celiac disease and inflammatory bowel disease, which might explain their coexistence (3). One of the diseases associated with tracheo-esophageal fistula anomalies especially esophageal atrophy is known to be EoE. These patients present with reflux symptoms refractory to treatment(4). Concurrent herpetic esophagitis in patients with EoE have been described since 1960 and pathophysiological mechanisms linking the two diseases have also been discussed (5). The pathophysiological mechanism of epithelial-mesenchymal transition induced by TGF-beta exists in both EoE and other fibroproliferative connective tissue diseases, thus associating both these diseases(6,7). Patients with cystic fibrosis have been known to be commonly associated with many gastrointestinal diseases such as gastro esophageal reflux disease and esophageal adenocarcinoma including EoE(8). Helicobacter pylori infection of the gut has been inversely associated with EoE with many possible mechanisms under discussion (9). Association of EoE with Barrett’s esophagus have also been reported and discussed with controversies (10).

Objective
This review intends to sum up all the disorders related with EoE to gain a wider knowledge about disease association. The knowledge thus acquired will help in early diagnosis of the disease and to deliver customized therapy resulting in a better therapeutic outcome.

Methods
This is a traditional review based on studies that were done to analyze any disease that has association with EoE. The search engines that were utilized for electronic data from the Internet were MEDLINE, PUBMED, GOOGLE SCHOLAR, OVID, EBSCOHOST and EMBASE using the search item “Eosinophilic esophagitis and associated diseases”.
All studies that related any disease to EoE worldwide on all time periods were included. All unpublished reports,
unavailable or unanalyzed or inaccessible articles from the internet sources that are supposed to constitute only 5% of the available resources by researches were excluded from the review. The keywords used while searching through all the selected databases were eosinophilic esophagitis along with associations and associated diseases/disorders.

**Results and discussion**

**Asthma**

Clinical experience and scientific studies have shown that majority of EoE patients have concomitant allergic diseases like allergic rhinitis, asthma and eczema. Adults and adolescents with EoE were found to be more associated with aeroallergen driven disease while children with EoE were associated with food allergen driven diseases. Allergic rhinitis has been found to be associated with 40-75% of EoE patients while 14-70% and 4-60% of EoE patients are found to be associated with asthma and eczema, respectively (11). In Genome-Wide Association Studies of Allergic Diseases done recently, TSLP (Thymic Stromal Lymphopoetin) region located in chromosome 5q22 was found to be associated with EoE. TSLP expression levels were found to be correlated with bronchial asthma as well (12).

EoE and asthma share a number of epidemiologic, clinical, pathological features and also share common therapeutic strategies. Both the diseases affect patients of all age group and begin in children and adolescents frequently. Even though EoE is more common in males and asthma is more common in females, asthma in children is more common in males than in females. Both are prevalent in western countries. Both are chronic immune mediated diseases exhibiting inflammatory changes in mucosa and submucosa with predominant eosinophilic infiltration resulting in remodeled airway/esophagus leading to organ dysfunction. Both the diseases respond to steroids; administered by inhalation in asthma whereas by oral route in case of EoE. All these similarities have led some to consider EoE as the asthma of the esophagus (13).

Presence of concomitant EoE, with or without dysphagia, in asthmatic patients can be predicted by certain clinical and laboratory characteristics like peripheral eosinophilia, atopic asthma and in patients who are not on steroids. These factors could be used to define a scoring system that might be used to strongly predict the presence of EoE in patients with asthma (14).

Thus, owing to the increased association of asthma with EoE, it is recommendable for all patients with asthma to be questioned for the presence of dysphagia and also investigated for the presence of predicting factors ensuring early diagnosis and effective treatment.

**Atopic dermatitis**

Given the strong association of EoE with allergic rhinitis and asthma, studies were conducted to see if atopic dermatitis is linked to EoE. Since, esophageal biopsy is not indicated in atopic dermatitis, Maria et al used monkey esophagus treated with serum of a patient with atopic dermatitis and demonstrated immunoreactivity patterns via indirect immunofluorescence. Strong staining patterns were detected for albumin, IgE, IgG, IgD, IgA, complement C1q and mast cell tryptase in the patient’s skin and also in monkey esophagus treated with patient’s serum, a broad intraepithelial staining pattern indicating an association between atopic dermatitis and EoE. The staining pattern of albumin was speculated as albumin to have become an allergen or it could be an immune modulator for the complex immune mechanisms involved in the disease (15).

**Atopic cataract**

Like other atopic diseases that are associated with EoE, a possible association of atopic cataract with EoE was also reported. Karthik and casson reported a case of bilateral atopic cataract in a 3.5-year-old boy who was previously diagnosed to have EoE at the age of 15 months. All the risk factors associated with the development of atopic cataracts were ruled out. Epidermal origin of the lens might make it vulnerable to atopic processes like other epidermal tissues or cationic proteins, like major basic protein released by eosinophils, might damage the lens, were the two mechanisms proposed for the development of atopic cataract in the patient (16).
Celiac disease
The association between celiac disease and EoE was first reported in 2007. Three cases of EoE with concomitant celiac disease were reported with one of the cases having responded to gluten free diet with reversal of histopathological features of EoE, suggesting gluten dependent EoE as a rare manifestation of celiac disease(17). Many studies reported the association between celiac disease and EoE later. A retrospective analysis of 250 pediatric cases of celiac disease was done in western Australia. Only 121 had concurrent esophageal biopsies done, the slides of which when reviewed revealed EoE in 10 cases. The prevalence of EoE in celiac disease patients was estimated to be 4% or higher, since not all the 250 cases had concurrent esophageal biopsy done. The prevalence thus estimated was higher than the prevalence of EoE in general population suggesting a non-coincidental association. The results imply the necessity to suspect EoE in all patients with celiac disease and the probable importance of esophageal biopsy in patients who undergo endoscopy for the diagnosis of celiac disease(18). Also larger cohort studies done in US and Canada imply that there is definite association between celiac disease and EoE(19,20). However, there are some studies that do not support the association. Lucendo et al investigated the presence of HLA DQ2 and DQ8 predisposing to celiac disease in adult patients with EoE. The prevalence of HLA DQ2 and DQ8 alleles in 78 EoE patients were compared with HLA genotyping of 421 healthy donors. No difference in prevalence was noticed between the subjects and controls implying that there is no common genetic basis between the two diseases(21). Further, in a comparative study, 120 celiac disease patients were investigated for the presence of EoE against 100 control subjects who underwent esophageal biopsy for causes other than celiac disease suspicion. No increase in prevalence of EoE was found in celiac disease patients in comparison with the control group indicating that the association between the two diseases is incidental(22). Although controversial studies exist, suspecting EoE in celiac disease patients and doing a concurrent esophageal biopsy might be beneficial to the patient until further evidence prove or disprove the association.

Schatzki rings
Schatzki ring (SR) is a radiological or endoscopic diagnosis, first reported in 1944, found in 6-14% of all routine barium radiographs done. SRs are mostly asymptomatic, episodic dysphagia for solid foods and food impaction being the most common presentations if symptomatic. They appear as thin circumferential fold of mucosa protruding into the lumen of the distal esophagus, 1-2mm thick, found at the squamocolumnar junction. The etiopathogenesis of SRs are unclear; theories relate their origin to congenital, anatomical and inflammatory factors(23,24).

In a prospective study conducted in 167 patients, newly diagnosed with SR, association with other esophageal disorders was analysed. 97% of SR patients showed the presence of sliding hiatal hernia. Other esophageal disorders found associated were erosive reflex esophagitis in 28.1%, esophageal webs in 15.6%, EoE in 5% and esophageal diverticula in 2.4% of the patients(23). Another report analysed 18 patients radiographically diagnosed as having SR and confirmed the presence of EoE in 8 patients histologically. But they were unable to locate the SR endoscopically in all the 8 EoE patients. Instead, they had all the gross features pertaining to EoE. The explanation given was SR in EoE is because of edema and eosinophilic infiltration extending into submucosa and muscularis propria causing infolding of the loosely adherent esophageal mucosa during contraction of the longitudinal muscle of the esophagus. The ring disappears when the longitudinal muscle relaxes also explaining the intermittent nature of symptoms in EoE. Thus, association of EoE with radiologically diagnosed SR was strongly suggested(24). Muller et al, in an analysis of 171 SR patients, found significant association between EoE and radiologically diagnosed SR but with inconsistent endoscopy findings(25).

Crohn’s disease
Suttar et al reported the first case of EoE in a 25-year-old female, with history of Crohn’s ileocolitis at the age of 17, treated medically and surgically. The patient had typical clinical, endoscopic and microscopic features of EoE. The association was attributed to the similar immune mechanisms involved in the pathogenesis of both the diseases (26). The profibrotic effect of eosinophil in Crohn’s disease had been proved already by invitro co-culture of intestinal fibroblasts from Crohn’s disease patients with human eosinophil sonicates(27). McIntire et al, studied the prevalence of Ulcerative colitis and Crohn’s disease in a cohort of 48947 patients who underwent both esophageal and ileocolic biopsies and stratified them with the number of esophageal eosinophils. Diagnostic eosinophil count being >15 per highpower field for EoE, prevalence of inflammatory bowel disease was twice in patients who had >60 esophageal eosinophils per high power field than patients with normal esophagus. Though case reports and studies suggest
positive association between EoE and Crohn’s disease, further investigations are required to confirm the association(28).

**Esophageal atresia**
Batres et al reported three cases of EoE who had the history of esophageal atresia, which was repaired soon after birth. The cases presented at the age range of 3-8 with features of anastomotic esophageal strictures. Esophageal strictures are seen in 5-15% of cases of esophageal atresia after repair, etiology being the tension placed on the anastomotic site owing to wide gap between the esophageal segments. Due to concurrent EoE, the strictures in all the cases were refractory to dilatation but responded to a diet devoid of allergic proteins(29). Gorter et al reported two cases of EoE who had esophageal atresia, which was repaired soon after birth. The cases presented with features of EoE at 2 and 4 years of age, which responded to diet restriction and steroid therapy. The cause for the association was attributed to the genetic similarities that exist between the two diseases. Forkhead box (FOX) transcription factor gene cluster is not only found to be associated with esophageal atresia in humans but also involved in inflammation especially related to eotaxin and interleukin 8 that play a major role in the pathogenesis of EoE(30). Dhaliwal et al, in a cohort of 113 esophageal atresia patients, identified the prevalence of EoE to be 17%, 38% of them presented with esophageal stricture at the time of diagnosis (31). Kassabian et al, reported 4 cases of EoE in esophageal atresia patients, highlighting the non- responsiveness of the condition for the treatment and reoccurrence of the esophageal stricture, unless eosinophilia is treated(32).

**Herpetic esophagitis**
There are case reports of EoE associated with herpetic esophagitis. Squires et al and Monsanto et al reported (3+1) cases which were diagnosed and treated for herpetic esophagitis, and later developed features of EoE. All the patients were immunocompetent, had history of atopy and presented with esophageal symptoms. Herpes infection was confirmed by Serological and histopathological examinations and the patients responded well to anti-viral therapy. Repeat endoscopy done for recurrent esophageal symptoms in a period of 1-2 months in all the reported cases showed features of EoE. The mechanism of association was explained as damage to the epithelium and loss of barrier function by herpes infection resulting in development of hypersensitivity leading to EoE. Also, herpes virus might have acted as a triggering agent to develop eosinophilic inflammation in the esophagus leading to EoE. The theory of presence of subtle EoE prior to herpetic esophagitis that might have increased the susceptibility to herpes infection was ruled out because of the absence of EoE features in all the patients at the time of presentation with herpetic esophagitis(33,34). Franulovic et al reported a case of EoE with concomitant herpetic esophagitis. Endoscopic and histological features confirmed EoE while herpetic esophagitis was confirmed by histological and serological tests(35). Thus, EoE and herpes esophagitis association appears to be significant and testing for either of the diseases if one of the diseases is diagnosed is advisable.

**Connective tissue diseases**
It has been well known that, the esophageal symptoms in EoE is due to subepithelial fibrosis caused by epithelial mesenchymal transition contributing to esophageal remodeling, and TGF-β (Transforming growth factor -beta), a profibrotic cytokine is known to play a major role in this process. Invitro treatment of esophageal epithelial cells with TGF beta causes upregulation of mesenchymal genes and esophageal biopsy tissues from EoE patients showed positive TGF beta immunostaining proving its role in EoE(36). Similarly, TGF beta has been known to be involved in the pathogenesis of many inherited connective tissue disorders (Marfan Syndrome, Loeys-Dietz Syndrome, Familial Thoracic Aortic Aneurysm and Dissection Syndrome, Hereditary Hemorrhagic Telangiectasia, Shprintzen-Goldberg Syndrome, Aneurysm-Osteoarthritits Syndrome and Arterial Tortuosity Syndrome). Given the role of TGF beta in the normal development and homeostasis of connective tissues, mutated TGF beta receptors, accessory receptors and related proteins are known to cause this group of inherited connective tissue diseases (CTD) also called as TGF beta dysregulation syndromes(37). Owing to the fact that TGF beta is involved in the pathogenesis of both EoE and inherited CTDs and also owing to the fact that EoE is increasingly seen in patients with CTDs, Adoni et al, analysed the rate of EoE in CTD patients and the possibility of defining new entity of patients with the co-existing conditions as EoE-CTD. They recorded an 8-fold increased risk of EoE in CTD patients compared to the general population strengthening the possibility of association between the two diseases and also discussed the therapeutic applications of the entity, given the recent developments in anti-TGF therapeutics(38).

Apart from inherited CTDs, there is another group of CTDs with autoimmune etiology that include systemic
sclerosis/scleroderma, rheumatoid arthritis and systemic lupus erythematosus. TGF beta, a potent regulator of extracellular matrix deposition, is involved in the pathogenesis of these autoimmune CTDs(37). The association of autoimmune CTDs with EoE is rare but not nil. There are very few cases that report possible association of EoE with rheumatoid arthritis. Sandhya et al reported a 38-year-old female patient with inactive rheumatoid arthritis who presented at the clinic with esophageal symptoms and then confirmed microscopically to have EoE. Although the association is rare, considering EoE in patients with inactive rheumatoid arthritis presenting with esophageal symptoms is suggested to ensure early diagnosis and treatment of these patients(39).

Cystic fibrosis
Cystic fibrosis (CF) has been known to be associated with gastrointestinal diseases like gastroesophageal reflux disease (GERD), distal intestinal obstructive syndrome and cholelithiasis. Goralski et al reported the first series of 3 EoE cases diagnosed in CF patients. All three patients presented with symptoms pertaining to GERD unresponsive to proton pump inhibitors and confirmed microscopically to have EoE. The pathogenesis of CF and EoE doesn’t overlap. Diagnosing EoE in CF patients presenting with gastrointestinal symptoms is difficult because of many other gastrointestinal diseases associated with CF presenting with similar symptoms and is important because undiagnosed and untreated EoE may further complicate the life of CF patients already complicated with lung disease and nutritional failure(40).

Helicobacter pylori infection
Helicobacter pylori (H. pylori) infection has been recently suggested to have inverse association with allergic diseases. Dellon et al set out to investigate the association between EoE and H. pylori infection. In a large cross sectional analysis of data collected from United States database of patients who underwent both esophageal and gastric biopsies, H. pylori infection was found to be reduced in patients with EoE when compared to patients with normal esophageal biopsies (41). Owing to decreased incidence of H. pylori infection and increased incidence of EoE in Japanese people, Furuta et al investigated if there exists an association between the two. In a cohort of 18 patients with EoE, the prevalence of H. pylori infection was 22.3% while 55.5% of the matched controls had H. pylori infection, confirming the inverse association between the two diseases. The reason was attributed to reduction in H. pylori infection leading to failure in activation of Th1 immune response resulting in imbalance between Th1 and Th2 immune response causing allergic diseases(42).

Barrett’s esophagus
The association between EoE and GERD along with subsequent Barrett’s esophagus had been complex and controversial. Ravi et al in a cohort of 200 patients with Barrett’s esophagus found the prevalence of EoE to be 7%(43). Saboorian et al in a large cohort of patients with Barrett’s esophagus reported that the patients with coexistence of the two conditions to be >0.2%. The reason attributed for association of the two conditions is GERD damaging the epithelial tissue increasing mucosal permeability causing the development of food allergy leading to EoE. Other reason suggested was regular use of proton pump inhibitors by GERD patients interfering the peptic digestion of food allergens favoring the development of EoE. The reason attributed for inverse association between the two conditions is the symptoms of EoE leading to changes in food habits by the patients that may reduce gastroesophageal reflux and consequently less Barrett’s esophagus, given the fact that the mean age of occurrence of EoE is less (44 years) than that of Barrett’s esophagus (63 years)(44).

Many diseases, both immune and non-immune mediated, have been found to be associated with EoE in varying degrees. This review gives a summary of the diseases associated with EoE. Diseases with inverse association and controversial association are also discussed. Also, possible mechanisms behind these associations are briefly described. This understanding might help to figure out better therapeutic options for the patients diagnosed with other diseases co-existing with EoE.

Table 1 – Eosinophilic esophagitis and associated conditions

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**Conflicts of interest**
There are no financial or other relations that could lead to a conflict of interest.

**Ethics**
This article does not contain any studies with human or animal subjects performed by any of the authors.

**References**


