Eosinophilic Esophagitis

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ABSTRACT

The frequency of eosinophilic esophagitis (EE) cases is increasing along with increased understanding among doctors about EE. In the beginning, EE is mostly found in children population. It was first reported in adults by Landres on 1978. The prominent EE symptoms in adults are dysphagia and solid food impaction. Endoscopic examination reveals mucous ring of esophagus, white plaque on the mucosa. The diagnosis is supported by positive result of eosinophils, which forms infiltration on the mucosaof > 20 eosinophils/ high power field in the distal or middle esophagus. Treatment by using diet and corticosteroid, either topical or systemic, shows adequate results. Immunomodulator treatment is promising, but it needs further investigation with larger sample. No consensus have been reached for EE, therefore it may affect the diagnosis, treatment and epidemiology data.

Keywords: *esophagus, eosinophil, dysphagia, ring of esophagus*

INTRODUCTION

Gastrointestinal tract is always associated with food, sometimes allergen and toxin; therefore eosinophil is naturally found in gastrointestinal tract. Esophagus is a unique part of gastrointestinal tract. Normally, there is no eosinophil found in esophagus. Some condition may cause eosinophil infiltration in esophagus, such as GERD, parasite infection, systemic eosinophilic syndrome, and a condition which is recently called as eosinophilic esophagitis.[1-3]

Eosinophilic esophagitis (EE) was first reported by Landres et al on 1978, after that there was an absent until in the mid-90's.[4] Since its clinical manifestation becomes more familiar to the gastroenterologists and allergists; EE has become important differential diagnosis for patients with esophageal symptoms. Consequently, there is greater amount of publication associated with EE and correlated to eosinophilic gastroenteritis, i.e. a condition, which has been known as a disease, associated with eosinophil and gastrointestinal tract.[3,4] Children and adults may be affected by EE. As a disease entity, EE may become diagnostic and therapeutic consideration, and may become a challenge either for pediatric gastroenterologist or common gastroenterologist.[1-3]

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EPIDEMIOLOGY

Epidemiologic data of EE has not been sufficient, because there is no consensus on EE, either about diagnosis criteria or treatment. Most of publications are case reports. It frequently occurs on children rather than adults, with incidence estimation in children and adults of $43/10^5$ and $2.5/10^5$ respectively. EE predominantly occurs in male than female.[2,5 6,7]

PATHOPHYSIOLOGY

Based on its clinical manifestation and immunologic characteristics, EE may be considered as 'asthma of the esophagus'.[1] Histological examination reveals a lot of eosinophils infiltration on the whole esophagus mucosa.[1-3,5-8]

Eosinophil derives from bone marrow and only a little amount of it appears in peripheral blood circulation. In a healthy person, it exists on lamina propria of gastrointestinal tract, except esophagus. Normal esophagus has no eosinophil infiltration. If there is eosinophil accumulation in esophagus, it indicates that there is a disease problem.[2,3,9]

Eosinophils in gastrointestinal tract will increase if

inflammation occurs.[3] Inflammation will cause eosinophils to infiltrate various organs such as lungs, esophagus, gastrointestinal tract and skin and it may have a role in organ damage and organ dysfunction.[3]

Hypothesis of food-induced EE is supported by observations of clinical symptoms and histological features in patients with EE who have been treated with diet therapy (food restriction and elemental diet supplement).[2,5,10] Observations on experimental animal have been conducted and these support that aeroallergen does induce esophageal and lungs inflammation through mechanism of cytokines.[10,11,12]

Induced eosinophils in esophagus and its increasing activity are caused by IL-5, eotaxin, II-13 and II-14. In EE, Th2 response and IL-5 production, the key of eosinophils congregation, in rats with less IL-5 receptor, significantly shows decreased eosinophils in gastrointestinal tract. Eotaxin in gastrointestinal tract has chemotaxis character.[4] It has been known that IL-4 and IL-13 may induce 'eosinophil-specific eotaxin' chemokines (eotaxin-1, eotaxin-2 and eotaxin-3). Its role has not been clear yet because we cannot show that in EE there is eotaxin overproduction; whereas decreased eotaxin-1 in rats only brings about moderate experimental EE. Gene that codes eosinophils chemo- attractant specified for eotaxin-3 (known as CCL 26) is the most induced gene in patients with EE. Rats with receptor eotaxin-3 deficiency were protected in experimental EE. These results supported the role of eotaxin-3 in the pathogenesis of EE disease, and EE is considered as a disease with important gene role.[11,13]

IL-13 is a pro-fibrotic cytokine, which is also produced by eosinophil. IL-13 in trachea may induce EE associated with lungs and esophageal inflammation. IL-13 appears to be a serologic indicator of systemic inflammation. IL-13 induced EE and depends on the presence of IL-5, eotaxin and STAT-6.[2]

Cysteinyl leukotrienes (CysLT) is an eosinophil chemo-attractant. The CysLT level of esophagus mucosa biopsy in children with AEE (Allergic Eosinophilic Esophagitis) is approximately similar to normal children and it does not depend on inflammation severity. We should consider the associated AEE treatment and CysLT antagonist. We need further investigation on CysLT receptor.[14]

Inflammation process may continue to chronic inflammation, which cause irreversible alteration on mucosa structure and elasticity as well as fibrosis in sub epithelial layer.[2]

DIAGNOSIS

The diagnosis of EE is based on patient's clinical manifestation, endoscopic and radiographic profile as well as histopathological criteria.[2,5] EE may affect children, mostly in 7-10 years old, and in adults between 30-40 years old. EE is predominant in male than female. Dysphagia symptom is frequently found in adult EE, while in children it usually manifest as abdominal pain. Other symptoms and signs are showed in table 1.[2,8] In children, it usually associated with history of allergic disorder, such as rhino-conjunctivitis, asthma, food allergy, eczema, or atopic dermatitis.[2,12]

Table 1. Clinical features of eosinophilic esophagitis [2]

	Adult	Pediatric
Common	Dysphagia Food impaction/foreign body Esophageal stricture Nausea/vomiting/regurgitation Heartburn Food allergy	Abdominal pain Failure to thrive Nausea/vomiting Dysphagia Food allergy Heartburn
Uncommon	Hematemesis Globus Water brash Weight loss Chest pain Abdominal pain	Food impaction
Associated conditions	History of atopy Asthma Allergic rhinitis	Asthma Allergic rhinitis Eczema Atopic dermatitis Strong family history of atopy

RADIOLOGY

Radiographic examination for EE includes barium imaging. Most patient with idiopathic EE show indentation image, which appears as multiple rings, stricture, esophagitis.[11] It may also indicate hiatus hernia and demonstrate a reflux (see figure 1).[2]

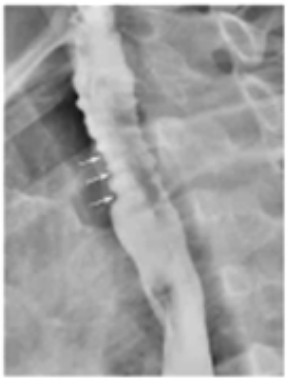

Figure 1. Single-contrast esophagogram (RAO view, patient was prone) indicates esophagus profile caused by eosinophilic esophagitis.[11]

ENDOSCOPY

A thorough endoscopic observation will reveal abnormality in most of EE patients (~90%).[1] The abnormality may appear as a ring-like image in esophagus or a concentric ring image in esophagus

(ringed esophagus), small esophagus caliber, with narrow internal diameter of esophagus, with or without stenosis in proximal esophagus (figure 2),[6] or appearing like stricture.[5-9,15] There is also 'multipel web' or 'corrugated ringed esophagus. Some authors detect a congenital stenosis esophagus, but it is often associated with EE. It is different from the Skatzki ring, which only has a single web in distal esophagus.[16] A vertical line may also found in esophagus.[2,6,7]

Sometimes, there is white exudates, vesicles or papule together with disappearing vascular image, which characterize the area of eosinophils infiltration (figure 2).[6] The esophageal mucosa membrane may become fragile, which is called as 'crêpe paper mucosa'.[2,6,7] Therefore, the mucosa is easily torn when we perform dilatation treatment.[2] A small sum of EE shows normal endoscopic profile.[2,17]

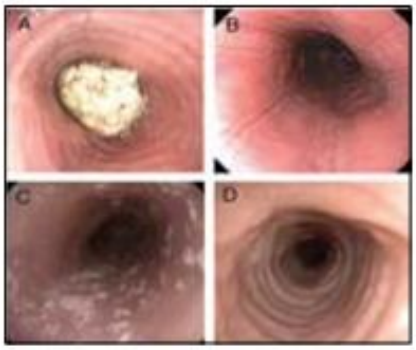

Figure 2. Endoscopic photographs showing common features of eosinophilic esophagitis[7]
A. Concentric mucosal rings seen throughout the length of the esophagus in a patient presenting with a food impaction.
B. Linear furrows or creases in the esophageal mucosa.
C. White exudates/plaques seen in some patients, which correspond to areas of eosinophilic abscess eruption through the esophageal mucosa.
D. Endoscopic photo of a patient with concentric mucosal rings and small caliber esophagus.

ULTRASONOGRAPH ENDOSCOPY

It is rarely performed to establish the diagnosis of EE. It is performed when there is a circumferential profile and asymmetric thickening in muscle layers.[2]

LABORATORY FINDINGS

Specific laboratory findings in patients with EE have not been reported, therefore the sensitivity and specificity of laboratory test has not been known yet. Eosinophilia in peripheral blood circulation may occur in 5%-50% adult EE patients. Increased IgE serum, positive 'skin prick' test or radioallergosorbent test (RAST) may be found in 40%-73% pasien.[2,12] Skin prick test and patch tests may identify the potential food, which may have important role in EE pathogenesis.[17]

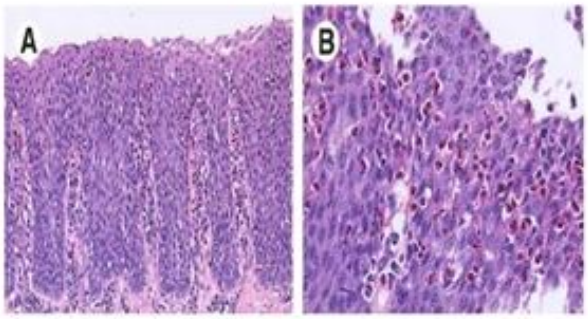

Figure 3. Pathological findings of esophagus mucosa in EE (A) Thickening of basal zone and intercellular edema (B) A lot of intraepithelial eosinophils (H&E staining).[1]

HISTOLOGICAL FINDINGS

Biopsy is recommended on proximal and distal esophagus. If endoscopic findings reveals white papule feature, then biopsy should be performed on that area, because it is the place where eosinophil congregated. [1,2,8]

The main histological findings in EE include eosinophil infiltration in esophagus. Hyperplasia in basal lamina and increased papillary size are not specific for EE. There is also increased eosinophils in GERD patients.[1,18,19] Some authors determine the 'cut-off value' of eosinophil infiltration to differentiate EE and GERD. In EE, either in children or adults, some authors determines eosinophil infiltration of > 15 eosinophils/ HPF-high power field (400 x), or > 20 eosinophil/HPF or > 30 eosinophil/HPF on squamous epithelium. While in GERD, there is less than 5 - 10 eosinophils/HPF. Other findings include positive eosinophils in the surface, which occasionally congregated and form a micro-abscess (i.e. 4 or more congregated eosinophils on the surface of esophagus epithelial). Micro-abscess is found in 25-45% of patients with EE, and it is never found in GERD patient.[1,2,5,8,17]

Table 2. Classification of esophagus disorder associated with eosinophil.[3]

Primary eosinophilic esophagitis	Secondary eosinophilic disorder	Secondary noneosinophilic disorder
(also known as idiopathic eosinophilic esophagitis and allergic esophagitis) o atopic o Non-atopic o Familial	o Eosinophilic gastroenteritis o Hyper-eosinophilic syndrome	o Iatrogenic eosinophilic esophagus o Infectious associated EE o Primary gastroesophageal reflux o Esophageal leiomyomatosis o Vasculitis (periaarteritis nodosa) o Connective tissue disease (scleroderma)

CLASSIFICATION

Eosiphilic Esophagitis classification is very confusing, one of its classifications is shown in table 2, as follows:

TREATMENT

There is no established guideline for EE treatment. The treatment may be classified into two categories, i.e. (1) prevent or remove eosinophil stimulant and (2) immune modulation.[2]

Diet and life-style modification

Diet and life-style modification is important in EE treatment, especially is there is evidence of food allergy. Allergy test may be performed as necessary. Foods that frequently cause allergy include: milk, egg, peanut, soybean, and fish. The patient may have allergy test such as skin prick test and patch test or aeroallergen test.[2,7,12,20] Foods known as allergic cause should be avoided. This diet modification is quite effective for children but it is less effective in adult EE case.[2]

Pharmacologic treatment

In addition to diet modification, pharmacologic treatment of EE has been challenging, considering that, there is no established study of EE pathophysiology and there is no agreement reached in diagnostic consensus.[2,16]

Either topical or systemic corticosteroid may be given. Fluticasone is local corticosteroid, which was given as 4 puffs of 220 ug, two times daily for 4 months period.[2,7]

Side effect such as dry mouth may occur. There was no oral candidiasis during the treatment.[2,7]

Systemic corticosteroid administered in the study included methyl-predinisolone 1.5 mg/kg orally twice daily for 4 weeks period, and subsequently tapped-off, and stopped after 6 weeks. The patients experienced clinical improvement with average improvement period of 8 days. All patients had histological improvement and decreased eosinophils amount and IgE in peripheral blood count. After 1-year follow-up, some patients had relapse. Some of them treated by diet modification and the others were treated by repeated corticosteroid treatment.[2,7] Comparison between topical corticosteroid and systemic corticosteroid treatment is ongoing.[2]

Montelukast is a selective inhibitor against LTD4 (leukotriene D4). Patients with EE were given 10 mg oral montelukast daily and then titrated to 100 mg daily, with maintenance dose of 20-40 mg/day. There were side effects of nausea and myalgia.[2,7,21]

Mepolizumab is a human monoclonal antibody, given to patient with idiopathic hyper-eosinophilic syndrome and EE who has no response to diet modification and oral corticosteroid treatment. Three doses of mepolizumab (10 mg/ kg IV) were administered with 4 weeks interval, and the patients were followed-up for 18 weeks. There was obvious symptoms improvement, There was also decreased peripheral eosinophil. No adverse events were found. There is no other study with larger number of participant has been reported.[2]

Prognosis

Accurate diagnosis and corticosteroid treatment (either topical or oral) combined with anti-reflux treatment result clinical and histological improvement. An 11-year observation of EE cases indicates no serious complication. We need further evaluation to investigate possibilities malignancies development of EE.[2]

CONCLUSION

More EE cases has been reported, a consensus on EE is extremely needed in order to reach the same perception. In addition to esophageal symptoms, esophageal biopsy in proximal and distal esophagus is essential for establishing diagnosis of EE. Diet modification is helpful. Topical or systemic corticosteroid can be used. In adult EE, topical corticosteroid appears to be more effective and comfortable. Immunomodulator treatment is promising. Combined therapy has not been explored. We need larger study to confirm the efficacy of treatment regimen.

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