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Eosinophilic Esophagitis and Eosinophilic Gastroenteritis: Similarities and Differences

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Eosinophilic gastrointestinal disease (EGID), a chronic allergic condition characterized by dense infiltration of eosinophils in the digestive tract, is classified into two types, eosinophilic esophagitis (EoE), which features dense infiltration of eosinophils in the esophageal epithelial layer, and eosinophilic gastroenteritis (EGE), in which the entire digestive tract including the esophagus may be involved. Patients with EoE only have esophageal symptoms, since the other parts of the digestive tract are not involved. On the other hand, 80% of EGE patients have lesions in the small intestine. The esophageal epithelial layer in healthy individuals has no or negligible infiltration by eosinophils, while the small intestinal mucosal layer, especially the distal small intestinal mucosa, can show dense eosinophil infiltration even in the absence of disease. Therefore, histological changes observed in cases of EGE are not qualitative but rather quantitative, as compared to EoE, which has qualitative histopathological changes, indicating important pathogenetic differences between the types. Comparisons of clinical, laboratory, and morphological characteristics between EoE and EGE have revealed several interesting differences. Both EoE and EGE patients are frequently affected by atopic diseases, such as bronchial asthma and allergic rhinitis, and elevated plasma levels of Th2 type cytokines and chemokines are also similarly seen in both. On the other hand, age at diagnosis differs, as the former is generally found in individuals from 30 to 50 years old, while the latter appears in all age groups. Additionally, 80% of patients with EoE are male as compared to only 50% of those with EGE. Furthermore, approximately 60% of patients with EoE respond favorably to proton pump inhibitor (PPI) administration, whereas EGE patients rarely show a response to PPIs. Nevertheless, both diseases show a similarly favorable response to a six foods elimination diet and glucocorticoid administration. These similarities and differences of EoE and EGE provide important clues for understanding the pathogenesis of these EGID types.

Key Words: Eosinophilic esophagitis, Eosinophilic gastroenteritis

INTRODUCTION

Eosinophils are known to be present in gastrointestinal tissue at various densities in the different segments of the gastrointestinal tract and have a variety of immune functions. In normal individuals, nearly no eosinophil infiltration can be found in the esophageal epithelial layer, while less than 10 eosinophils are observed in 400× high-power magnification fields in the mucosal subepithelial and submucosal layers of the stomach and duodenum.[1] The number of infiltrating eosinophils in the mucosal layer increases along the gastrointestinal tract and then reaches maximum in the distal ileum and right side of the colon. In the left side of the colon and rectum, the number of infiltrating eosinophils decreases to less than 5 in a 400× high-power magnification field.[1] When increased eosinophil infiltration density is found in gut tissue, the presence of eosinophilic gastrointestinal disease (EGID) must be considered.

EGID can be defined as an allergic disease that features dense infiltration of eosinophils in the gut, with resultant morphological and functional abnormalities. The disease is divided in two major groups, including eosinophilic esophagitis (EoE), characterized by dense eosinophil infiltration only in the epithelial layer of the esophagus, and eosinophilic gastroenteritis (EGE), which has dense eosinophil infiltration in the stomach and intestine irrespective of the presence of

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Table 1. Similarities and Differences of EoE/EGE

	Common in EoE/EGE	EoE	EGE
Pathogensis	Th2 immune reaction	Higher acid secretion	
Diagnosis	CT Histopathology	Endoscopy	CT ascites
Treatment	Steroid/Topical steroid	PPI/P-CAB	Unmet needs

EoE: eosinophilic esophagitis
EGE: eosinophilic gastroenteritis

esophageal eosinophil infiltration.[2] The rates of incidence and prevalence of EoE have been reported to be increasing, especially in developed countries, and those are higher as compared to EGE.[2,3] In Japan, the prevalence of EoE is now five times higher than that of EGE.

Although EoE and EGE have similar pathogeneses and clinical characteristics, there are several important differences between them. In this review, we will focus on their similarities and differences in order to characterize these two EGIDs (Table 1).

Pathogenesis

EoE and EGE are frequently accompanied by allergic/atopic diseases, with approximately 50% of affected patients reported to have bronchial asthma, allergic rhinitis, food allergy, and/or atopic dermatitis.[2] In addition, microarray analyses of mRNA extracted from biopsy samples obtained from esophageal and gastric mucosa of EoE and EGE cases have revealed that increased mRNA production related to Th2-type T cell immune response occurs in both, with IL-4, -5, -13, and eotaxin3 mRNA contents reported to be significantly increased in gut mucosal tissue.[4,5] These observations strongly suggest a relationship of allergic background with development of EoE and EGE. Bacterial infection including *Helicobacter pylori* is reported to stimulate Th1-type and suppress Th2-type immune response. We previously investigated the rates of *H. pylori* infection in EoE and EGE patients, and compared the findings with those obtained with age- and gender-matched controls, which clearly showed that the rate of *H. pylori* infection was significantly decreased in both EoE and EGE cases.[6] In addition, studies performed in different areas throughout the world have found inverse correlations of *H. pylori* infection rate with EoE prevalence. For example, in northern European countries, the prevalence of EoE was found to be high and rate of infection low, whereas that prevalence has been found to be low and the rate of *H. pylori* infection high in African countries.[7] These results suggest an important role of Th2-type immune response in development of EoE and EGE.

For development of EoE, additional factors may also be involved. The male/female ratio of cases with EGE is known to be 1:1, with no significant gender-related differences reported. On the other hand, in our study we found that the prevalence of male gender in EoE cases was much higher than that of females, with approximately 80% of affected patients male.[2,8] The reason for this difference in gender ratio between EoE and EGE has not been clarified, and the presence of additional augmenting factor(s) only occurring in males is possible. When gender ratio was compared between non-elderly and elderly EoE patients, male preponderance was only found in the non-elderly group, while the ratio of males to females in the elderly was approximately 1:1, as seen in cases of EGE. Non-elderly males without *H. pylori* infection have higher levels of gastric acid secretion than elderly males and all females.[9] Reflux of highly acidic gastric contents in the esophagus and the resulting increased permeability of the distal esophageal mucosa may be an additional pathogenetic mechanism for development of EoE. The greater amount of gastric acid secretion observed in non-elderly males without *H. pylori* infection in addition to an augmented Th2-type immune reaction may be responsible for the high male/female gender ratio seen in non-elderly EoE cases.

Diagnosis

Symptoms reported by patients with EoE differ from those with EGE, possibly because of differences of related gut lesions. The most frequently noted symptom in EoE cases is dysphagia, reported by approximately 50% of affected patients, followed by heartburn and epigastralgia.[2,3] Dysphagia may be caused by esophageal fibrous stenosis, mucosal edema, and/or impaired esophageal motor functions. As for EGE patients, more than 50% report abdominal pain and diarrhea as chief complaints. Since 80% of EGE cases have lesions in the small intestine, abdominal pain and diarrhea are expected symptoms in affected cases.[2]

Presently available laboratory blood, urine, and fecal tests do not have adequate sensitivity or reliability. Approximately one-third of EoE patients show peripheral eosinophilia, while 80% of those with EGE show eosinophilia, thus the presence of peripheral eosinophilia is not useful as a marker for diagnosis of EoE.[2] Additionally, neither plasma total nor antigen-specific IgE concentrations have adequate reliability for diagnosis, as values for those have been shown to have large

variations among EoE and EGE cases, and control groups, thus decreasing the value of plasma IgE concentration as a biomarker of either EoE or EGE.[10] On the other hand, though not routinely measured in clinical practice, we generally examine plasma Th2-type cytokine concentrations, as IL-5 and -15, and eotaxin3 concentrations have been found to be elevated in some EoE and EGE cases.[11,12] However, because of the large overlaps seen between patients and controls, these Th2 cytokine plasma concentrations do not seem to be adequate for use as markers for diagnosis of EGID. More sensitive and reliable biomarkers for diagnosis as well as disease severity evaluation are anticipated.

Clinical imaging is considered to be more useful for detecting evidence of EoE and EGE, with a majority of EoE cases reported to show thickening of the wall of the esophagus and a majority of EGE cases showing such thickening in the gut.[2] Segmental wall thickening in the small intestine is a characteristic finding of EGE, with ascites collected near the involved gut segment also frequently observed. Thus, computed tomography is a reliable method for detecting the possible presence of EoE and EGE.

Upper gastrointestinal endoscopy findings are also considered reliable for diagnosis of EoE,[13-15] with various characteristic abnormalities reported. Longitudinal furrows, white plaque, and concentric rings are the most frequently observed endoscopic abnormalities, and found in more than one-third of affected patients. Notably, one-third of those with linear furrows will be finally diagnosed as EoE. We have presented a novel endoscopic finding useful for EoE diagnosis as well as prediction of favorable effects of proton pomp inhibitor (PPI) administration.[16] It has been noted that some cases of EoE show multiple white nodules arranged on the esophageal mucosa in longitudinal lines, which represent thickened esophageal epithelium and have an appearance similar to nodules on the back of a dinosaur. Thus, this endoscopic finding is termed Ankylosaurus back sign (ABS) and has been proposed to be a good marker for selecting treatment options for EoE. In patients with EGE, various abnormalities, including erythema, edema, erosions, and ulcers, are frequently found in endoscopic examinations of gastric and intestinal mucosa.[2] However, there is a lack of specificity regarding those findings, thus EGE diagnosis based solely on endoscopic findings is not easy. As a result, endoscopy is considered to be a reliable diagnostic method only for diagnosis of EoE, while computed tomography is thought to be equally useful for diagnosis of both.

Histopathological results are required for definitive diagnosis of EoE as well as EGE. Although dense infiltration of eosinophils greater than normal is a necessary finding, papilla elongation, a thick basal layer, dilated intracellular spaces, and subepithelial fibrosis are also useful for evaluation of patients suspected of having EoE.[17]

Treatment

Various treatment options are available for treatment of EoE and EGE. Since both are allergic diseases caused by augmented Th2-type immune activation, mainly by food allergens, food allergen elimination or amino acid elemental diets are considered to be effective, with the latter shown to be effective in 70% of patients. Similarly, six-food elimination diets that exclude wheat, milk, egg, soy, nuts, and seafood produces have been reported effective in over 70% of EoE cases.[18] As for EGE treatment, the results of several case reports including ours have suggested benefits of an elimination diet, though the level of evidence provided in those reports is not considered to be adequate.[19,20]

For treatment of EoE, but not EGE, PPI administration is known to be effective.[21] However, administration of a double-dose PPI for longer than 2 months causes symptomatic, endoscopic, and histopathological healing in at least half of EoE cases. Furthermore, the mechanisms by which PPIs cause beneficial effects are not thoroughly understood. On the other hand, use of vonoprazan, a potassium competitive acid blocker and more potent acid inhibitor, has been reported to induce healing in nearly 50% of patients with PPI-resistant EoE.[22] This observation suggests a role of gastric acid in development of EoE, and may explain why the greater potency and complete acid inhibition seen with vonoprazan results in a better healing rate.

For both EoE and EGE, glucocorticoid administration is considered to be an effective treatment option. Topical glucocorticoids including fluticasone and budesonide have been shown adequately effective for EoE.[23] When ingested, these agents attach to the esophageal mucosa surface and have an anti-inflammatory effect. After absorption through the small intestine, topical glucocorticoids are rapidly and nearly completely degraded in the liver during the first path, and show minimal systemic adverse effects. Over 70% of EoE cases can be satisfactorily controlled by such administration, though interruption of treatment leads to recurrence of disease activity in nearly all cases. As for EGE, systemic steroid treatment, mainly prednisolone, is the most frequently selected option. Although glucocorticoids are at least temporarily effective for treatment of the majority of EGE cases, two-thirds show

secondary resistance or recurrence during the maintenance or dose-reduction phase.[24] The effects of topical glucocorticoids for EGE have not fully investigated and additional studies are needed.

The roles of anti-allergic drugs and neutralizing antibodies against various cytokines have recently been actively investigated. Montelukast,[25] an anti-TNF alfa antibody, as well as an anti-IgE antibody[26] were shown to be ineffective for treatment of EoE, whereas anti-IL5[27] and anti-IL13 antibodies[28] were found effective for symptomatic and histopathological control of EoE. Nevertheless, future studies including those with larger cohorts are necessary.

EoE and EGE Similarities and Differences

There are some important similarities between EoE and EGE, while differences have also been found. As for pathoge nesis, an augmented Th2 immune reaction is a fundamental abnormality seen in both, while esophageal mucosal exposure to highly acidic gastric juice is considered to be important in cases of EoE but not in those of EGE. Computed tomography and histopathological examination results are useful for diagnosis of both EoE and EGE, whereas endoscopy is not so helpful for diagnosis of EGE because of its non-specific findings, which is different from EoE. For treatment, elimination and elemental diets as well as administrations with glucocorticoids are effective options for EoE and EGE, with acid inhibitors including proton pump inhibitors and the potassium competitive acid blocker vonoprazan effective for only EoE.

CONCLUSION

EoE and EGE are EGID entities that feature development of lesions in different segments of the alimentary tract. They share several characteristics, while there are also some important differences between them.

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