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Eosinophilic Esophagitis and Proton Pump Inhibitor-Responsive Esophageal Eosinophilia: Single Center Experience

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ABSTRACT

Objective: Eosinophilic esophagitis is a chronic inflammatory disease characterized by eosinophilic infiltration and esophagus dysfunction symptoms. Proton pump inhibitor responsive esophageal eosinophilia is similar to eosinophilic esophagitis in terms of clinical, laboratory, genetic expression profile, endoscopic and histopathological features. In this study, we aimed to share demographic features, clinical, laboratory and histopathological findings, and treatment outcomes of patient with eosinophilic esophagitis and proton pump inhibitor responsive esophageal eosinophilia.

Materials and Methods: Demographic features, laboratory, endoscopic and histopathological findings, and treatment outcomes of patients followed in our clinic were recorded retrospectively since January 2010.

Results: Four thousand six hundred fifty five patients underwent esophagogastroscopy since 2010 in our clinic and 0.4% (n=18) of these patients were diagnosed with eosinophilic esophagitis, and 0.2% (n=8) with proton pump inhibitor-responsive esophageal eosinophilia. The main symptom of patients with eosinophilic esophagitis were food impaction/dysphagia (n=5, 27.8%) and chronic abdominal pain (n=5, 27.8%). Allergen sensitization was found in 14 (77.8%), increased IgE in 12 (66.7%), peripheral eosinophilia in 12 (66.7%), and food allergen sensitization in 10 patients (55.6%) with eosinophilic esophagitis. On histopathological examination, the mean intraepithelial eosinophil count was 48.9 ± 30.9 cells / HPF (400x). When patients with eosinophilic esophagitis (group 1) and proton pump inhibitor-responsive esophageal eosinophilia (group 2) were compared, it was found that chronic abdominal pain was more common in the proton pump inhibitor-responsive esophageal eosinophilia group and food allergen sensitization in the eosinophilic esophagitis group ($p<0.05$). Total IgE, peripheral eosinophil count and intraepithelial eosinophil count were higher in the eosinophilic esophagitis group, but the differences were not statistically significant. Diet (n=11), medical (n=17) and dilatation (n=1) therapies were used in the eosinophilic esophagitis group. Fibrosis was detected on the histopathological examination in two patients who underwent TED and then SED was started. No side effect was seen any group in long term.

Conclusion: Eosinophilic esophagitis and proton pump inhibitor-responsive esophageal eosinophilia have similar laboratory and histopathological features but eosinophilic esophagitis should be suspected more frequently in the presence of food allergy. Long-term follow-up is essential in patients with eosinophilic esophagitis.

Key words: Child, eosinophilic esophagitis, food allergen sensitization

INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic inflammatory disease characterized by eosinophilic infiltration and esophagus dysfunction symptoms such as dysphagia, food impaction/dysphagia, retrosternal pain and vomiting (1). The incidence of the disease has increased in recent years and studies have reported an incidence of 10/10.000 and a prevalence of 10-57/100.000 (2). EoE is more common in socioeconomically developed countries, male gender and the childhood period. In addition, risk factors such as genetic susceptibility, dysbiosis, exposure to smoking and

antibiotics during the first few years of life, and cesarean section have been associated with EoE (3).

Increased epithelial permeability due to disruption of the esophageal epithelial barrier that results in the initiation of an inflammatory process with triggering of T cells by allergens is accused for the pathogenesis. Release of cytokines such as interleukin (IL)-13, IL-4 and IL-5 increases with the triggering of the T helper 2 cells, resulting in increased expression of eotaxin-3 and eosinophilic inflammation (4). Tissue damage further increases due to the chemokines released by eosinophils, and complications ranging from fibrosis to narrowing may develop (5).

The diagnosis of EoE is based on clinical and histopathological findings. Besides esophageal dysfunction findings, it is defined by presence of 15 or more eosinophils per high-power field (HPF) (400x) in esophageal biopsy and histopathologically persistent numbers of intraepithelial eosinophils after 6-8 weeks of proton pump inhibitor (PPI) therapy (6). In addition, other diseases that may cause esophageal eosinophilia (EE) such as achalasia, connective tissue diseases, infections, Crohn's disease, PPI-responsive esophageal eosinophilia (PPIREE), gastroesophageal reflux disease (GERD), celiac disease, drug sensitivity and vasculitis should be considered in the differential diagnosis (7).

Proton pump inhibitor-responsive EE has been described for the first time in 2006, and is similar to EoE in terms of clinical, endoscopic and histopathological features. Eosinophilic infiltration occurs as a result of the release of eotaxin-3 proteins as in EoE. Eosinophilic infiltration is resolved by PPI due to suppression of gastric acid secretion and eotaxin-3 release. The difference between PPIREE and EoE is clinical and histopathological improvement after PPI treatment in PPIREE (<15/HPF) (8).

In this study, we aimed to share demographic features, the clinical, laboratory and histopathological findings, and treatment outcomes of patient with EoE and PPIREE who we followed-up at our clinic.

MATERIALS and METHODS

Demographic features, laboratory findings [peripheral eosinophil count (PEC), immunoglobulin E (IgE) and skin prick test/food specific IgE], endoscopic and histopathological findings, treatment modality and outcomes of the patients with EoE and PPIREE seen at the Pediatric Gastroenterology Unit since January 2010 were recorded. Patient data were obtained by retrospective screening of the hospital files.

Eosinophilic esophagitis was defined as the presence of more than 15 eosinophils per HPF (400x) in the histological examination, and persistent EE despite high-dose (2 mg/kg) PPI treatment for 6-8 weeks. PPIREE was defined as <15 eosinophils/HPF (400x) in the histological examination performed after 6-8 weeks of high-dose (2 mg/kg) PPI treatment (6,8). The mean intraepithelial eosinophil count (IEC) was determined by examination of esophageal biopsy samples of all patients by a pathologist. A skin prick test and/or food-specific IgE test was performed in patients by the pediatric allergy specialist in order to define the triggering allergen. A serum food-specific IgE test outcome > 0.35 kU/L was considered significant. Peripheral eosinophilia (>300 cells/μL) was determined with a complete blood count. The upper limit of IgE values was evaluated according to age (9).

Treatments of the patients were decided by the physician who followed-up the patient, considering the presence and number of positive tests for food allergy. Patients who had severe clinical symptoms and/or severe endoscopic-histologic findings were treated with systemic corticosteroids. Oral systemic corticosteroids (SCS) were initiated at a dose of 1 mg/kg (maximum 60 mg). After suppression therapy of two weeks, the dose of the steroids was gradually decreased, and they were discontinued in 6-8 weeks. Whereas topical corticosteroids (TCS) were initiated as budesonide 1 mg/day or fluticasone propionate 440 mcg-880 mcg/day (range 3-12 months). In TCS therapy longer than 3 months, the dose was decreased (0.25 mg budesonide, 125 mcg/day fluticasone propionate). A targeted diet (TED) was administered by the elimination of allergens detected in the skin prick or serum specific IgE tests, and six elimination diets (SED) were applied with the elimination of cow's milk, egg, soy, wheat, peanut/tree nuts and fish. Amino acid-based infant formula was used in the elemental diet (ED).

Ethics committee approval was not necessary due to the retrospective vision of the study. Informed and verbal consent was obtained from the parents prior to the endoscopic procedures.

Data for the statistical calculations are expressed as mean ± standard deviation (SD) in the continuous variables, and percentage (%) in the categorical variables. In comparison of the quantitative data of the group, the Stu-

dent t test was used in normally distributed and the Mann-Whitney U test in non-normally distributed data. The chi-square test was used in the comparison of the qualitative data. p values < 0.05 were considered significant.

RESULTS

Since January 2010, 4655 patients underwent esophagogastroscopy and 0.4% (n=18, 95% CI, 0.2-0.6) of these patients were diagnosed with EoE, and 0.2% (n=8, 95% CI, 0.08-0.32) with PPIREE. The main symptom of EoE patients (mean age ± SD; 7.5 ± 4.7 years, 83.3% male) was food impaction/dysphagia (n=5, 27.8%) and chronic abdominal pain (n=5, 27.8%), and feeding problems were detected in four patients (22.2%), retrosternal pain in two patients (11.1%) and vomiting (5.6%) and upper GIS bleeding (5.6%) each in one patient. There was no asymptomatic patient. Allergen sensitization was found in 14 patients (77.8%), high IgE in 12 patients (66.7%) and peripheral eosinophilia in 12 patients (66.7%). Food allergen was found in 10 patients (55.6%) [cow's milk (n=8), egg (n=5), soy (n=4), hazelnut and walnut (n=3), wheat and kiwi (n=2), rice, fish, peanut, corn, flour, spice and sesame (n=1)] aero-allergen in eight patients (44.4%) and venom allergen in one patient (5.6%). The most common finding in esophagoscopic examination was white exudates/ulcer (n=6, 33.3%), while linear furrows, trachealization, white spot lesions (n=2, 11.1%), erosion and structure (n=1, 5.6%) were among the other findings. The esophagus appearance was normal in 4 patients (22.2%). On histopathological examination of esophageal tissue samples, the mean IEC was 48.9 ± 30.9 cells / HPF (400x) (range: 19-125 cells / HPF). Fibrosis and superficial eosinophilic layer was present in two patients (11.1%) and eosinophilic abscess in one patient (5.6%) with EoE. No patient had lymphocyte infiltration, spongiosis or basal cell hyperplasia in the biopsy materials.

The main symptom of eight patients with PPIREE was chronic abdominal pain (n=6, 75%) accompanied by increased IgE and peripheral eosinophilia at 50%. Among these patients, allergen sensitization was detected in four patients (50%), aero-allergen in three, nuts and egg allergens in one patient, while no cow's milk, soy, peanut, walnut, kiwi, rye and wheat sensitization was found in patients with PPIREE. Allergen sensitization of both groups is shown in Figure 1.

When the patients with EoE and PPIREE were compared, it was found that chronic abdominal pain was more common in patients with PPIREE, and food allergy in patients with EoE (75% *vs.* 27.8%, p=0.02 and 12.5% *vs.* 55.6%, p=0.04 respectively). Although the presence of allergen sensitization and total IgE, PEC and IEC were higher in the EoE group, the differences were not statistically significant (p>0.05). Demographic, clinic and laboratory characteristics of both groups are shown in Table I. Multivariate analysis was not possible due to the small number of patients.

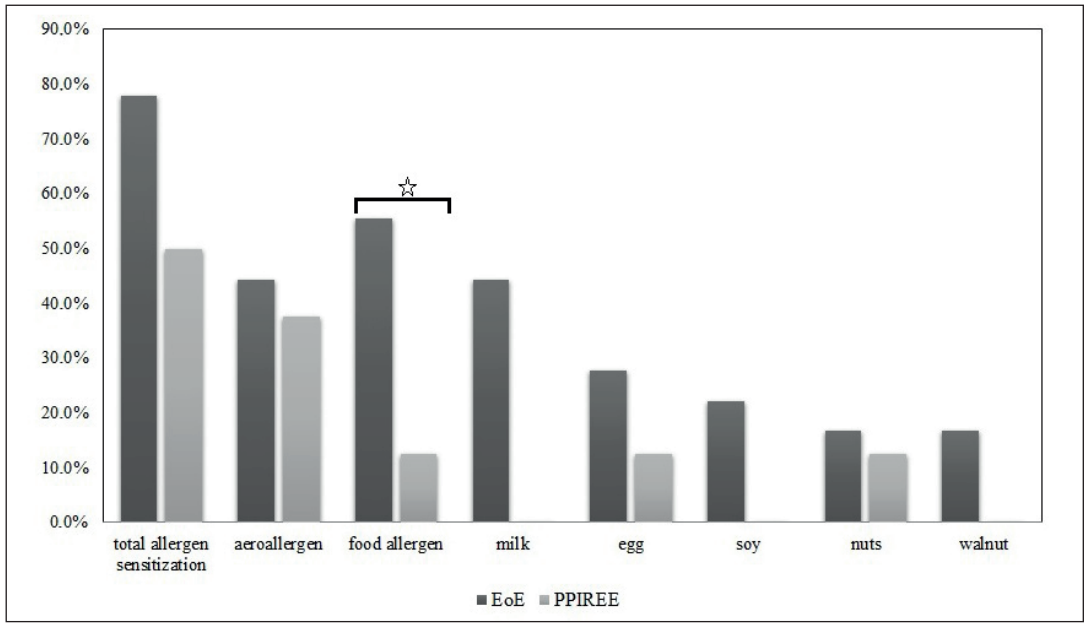

Figure 1. Allergen sensitization of patients with EoE and PPIREE.
EoE: Eosinophilic esophagitis,
PPIREE: Proton pump inhibitor-responsive esophageal eosinophilia.
*: p<0.05

In the treatment of patients with EoE; TED (n=5), SED (n=5), ED (n=1), and/or CS [systemic (n=11), topical (n=5)] therapies were administered. Esophageal dilatation was performed in addition to medical and diet therapy in one patient due to narrowing. During the follow-up, fibrosis was detected on histopathological examination under TED treatment and SED was applied later. Additionally, fibrosis occurred in another patient under TED and then SED was applied.

During the mean follow-up duration of 40.6 ± 25.7 months (4-96 months), four patients were CS and diet free (cured), while five patients were receiving TED, two patients SED, one patient low dose SCS, one patient TCS+SED, one patient SCS+SED and one patient TCS. One patient was lost due to sepsis and two patients were lost from follow-up. Demographic, laboratory and post-diagnostic endoscopic findings and treatment outcomes of all patients are shown in Table II and Table III.

Control endoscopy revealed histopathological improvement in patients with PPIREE after high-dose PPI treatment for 6-8 weeks. These patients used PPI for 4.43 ± 3.35 month on average. One patient underwent an antireflux operation since reflux symptoms could not be controlled with medical therapy.

During the follow-up of patients with EoE and PPIREE, no side effect was seen due to medical treatment or diet elimination.

DISCUSSION

In this study, we observed that EoE and PPIREE have similar laboratory and histopathological features, but food allergen sensitization was more common in EoE. EoE is a disease progressing with complications and requiring longer duration of follow-up.

It is difficult to phenotypically distinguish PPIREE from EoE. It has many similar clinical and laboratory features, and it is also genotypically similar (10). In a study, it was found that the levels of CCL26 (eosinophil chemotaxis), CPA3 (mastocytosis), MUC4 (IL-13 responding) and POSTN (tissue remodeling) chemokine proteins that are high in EoE and cause eosinophil migration were at similar levels in PPIREE and were low in GERD (11). In another study, patients with EoE and PPIREE were compared, and it was found that food allergen sensitization, atopic disease and the rate of high total IgE were higher in patients with EoE, while IEC, endoscopic appearance and the rates of clinical findings were similar (12). In our patients, food allergen sensitization was significantly higher in patients with EoE. However, although IEC, PEC, and total IgE

Table 1: Demographic, clinic and laboratory characteristics of patients with EoE and PPIREE.

Parameters	EoE patients (n=18)	PPIREE patients (n=8)	p
Age (years) mean ± SD	7.5 ± 4.7	8.8 ± 3.6	0.49
Male sex n (%)	15 (83.3)	5 (62.5)	0.24
Allergen sensitization n (%)	14 (77.8)	4 (50)	0.15
Aeoro-allergen	8 (44.4)	3 (37.5)	0.7
Food allergen	10 (55.6)	1 (12.5)	**0.04**
Allergic disease n (%)	7 (38.9)	2 (25)	0.49
Allergic asthma	6 (33.3)	1(12.5)	0.26
Allergic rhinitis	1 (5.6)	1 (12.5)	0.53
Main symptoms n (%)			
Chronic abdominal pain	5 (27.8)	6 (75)	**0.02**
Food impaction / dysphagia	5 (27.8)	0	
Vomiting	1 (5.6)	2 (25)	0.15
Acute retrosternal pain	2 (11.1)	0	
Nutritional problems	4 (22.2)	0	
GIS bleeding	1 (5.6)	0	
Increased total IgE	12 (66.7)	4 (50)	0.4
IEC (cell/HPF) mean ± SD	48.9 ± 30.9	31.4 ± 32.5	0.2
Peripheral eosinophilia (>300 cells/μL)	12 (66.7)	4 (50)	0.4

EoE: Eosinophilic esophagitis, **IEC:** Intraepithelial eosinophil count, **GIS:** Gastrointestinal system, **HPF:** High-power field, **PPIREE:** Proton pump inhibitor responsive esophageal eosinophilia.

values were higher in patients with EoE, the differences were not statistically significant. The clinical findings were different in our patients than in the previous study. We thought that this may be due to the different age groups of the patients in the two studies.

Because EoE is a long-lasting condition where treatment requires patient compliance, the phenotype of the disease (stenotic, inflammatory) and the preferences of the patient and the physician should be taken into account. Medical therapy, diet and dilatation are among the treatment methods (6). We decided on the treatment modality for our patients according to the presence of positive allergic tests and the severity of the clinical symptoms.

Studies have found that antiallergic drugs used in medical therapy (antihistaminics, cromolyn sodium, montelukast) are not effective while studies on biological agents are continuing. CS combined with diet therapy is known as the optimal treatment method. According to recent studies, the use of SCS has no superiority to TCS and has a higher rate of recurrence and side effects with drug discontinuation (13). The majority of our patients used diet combined with CS. SCS was only administered to patients who had severe clinical symptoms and/or severe endoscopic-histological findings and stopped quickly. Besides, five patients used TCS for a long time but no acute side effect such as adrenal suppression, moniliasis, osteoporosis, or cushingoid face was observed in our patients.

Diet therapy is an inexpensive, safe and effective method. Although it has the highest effectiveness, ED is the most difficult diet to administer due to the taste problem, and the cure rate with this method was found to be 90%. SED is effective in about three-fourths of the patients. Although it has a taste advantage compared to ED, patients present with problems in treatment compliance because of the need for repeated endoscopy and the large number of restricted foods. TED is not recommended often because of its low cure rate and low positive predictive values (13%) of the test used (6). In a large review by Arias et al., 1317 EoE patients (1128 children, 189 adults) were investigated; ED, SED and TED were administered to patients with EoE and the cure rates were found to be 90.8%, 72.1% and 45.5%, respectively (14). Recently, the

Table II: Demographic, clinical and laboratory findings of the patients with EoE.

Patients no	Sex / Age	Main Symptom	Allergen sensitivity	PEC / Total IgE
1	M /12 y	Food impaction / dysphagia	*Df, Dp*	55 / 399
2	M / 9y 9m	Food impaction / dysphagia	Milk, Egg	310 / 99
3	M / 20 m	Vomiting	Milk	1280 / 292
4	M / 10 y	Abdominal pain	Negative	197 / 51
5	M / 8 y	Abdominal pain	Negative	318 / 460
6	M / 12 y	Retrosternal pain	*Df, Dp*, Milk, Eggs, Soy	150 / 1037
7	M / 3y 10m	Abdominal pain	*Dp, Df*	390 / 600
8	M / 3y 7m	Feeding problems	Fish, Rice	130 / 254
9	F / 14 y 4m	Bloody vomiting	Negative	90 / 80
10	F / 26 m	Feeding problems	*Dp, Df,* Egg	1270 / 174
11	M / 13 y	Retrosternal pain	Walnut, Kiwi, Banana, Milk, Egg, Nuts, Rye, Spice, Sesame, Maize, Meadow, Walnut, Soy	70 / 2500
12	M / 8 y 4m	Food impaction / dysphagia	Milk	560 / 93
13	M / 5y 10m	Abdominal pain	Milk, soy, nuts, walnuts, grass, rye	473 / 1093
14	M / 13 y	Abdominal pain	*Df, Dp,* meadow, phadiatop	550 / 338
15	F / 24 m	Food impaction / dysphagia	Negative	434 / 60
16	M / 26 m	Feeding problems	Milk, Egg	460 / 190
17	M / 4y 8m	Feeding problems	*Df, Dp*, soy, nuts, pistachio, flour, walnut, kiwi	890 / 1200
18	M / 14 y	Food impaction / dysphagia	Venom	650 / 2000

Df: *Dermatophagoidesfarinae*, **Dp:** *Dermatophagoidespteronyssinus*, **IEC:** Intraepithelial eosinophil count, **M:** Male, **PEC:** Peripheral eosinophil count.

step up diet treatment method is used in some centers. This method, in which first two (milk, gluten), and then four or six diet elimination is used according to clinical and histopathological improvement, requires less diet restriction and endoscopic procedures and thus treatment compliance is increased (15). In our study, TED was used in five patients and fibrosis occurred in two patients under TED treatment. These patients were then treated with SED and CS during the follow up.

In this retrospective study; the main limitation is the lack of a diagnostic test (24 hour pH monitorization or impedance) for differentiating PPIREE from reflux-related EE.

In conclusion, EoE and PPIREE have similar laboratory and histopathological features except for food sensitization that is more common in EoE. Additionally, EoE is a chronic inflammatory disease that progresses with relapses and may cause long-term complications. To find the optimal and practical treatment method for these patients is important for treatment compliance. A multidisciplinary treatment approach is needed with the involvement of a pediatric gastroenterologist, dietician and pediatric allergy specialist in order to improve the patients' long-term quality of life and to avoid treatment complications.

Table III: Post-diagnostic endoscopic-histological findings and treatment outcomes of patients all patients.

Patients no	1st endoscopy findings	IEC (cell/ HPF)	Treatment	2nd endoscopy findings	IEC (cell/ HPF)	Treatment	3rd endoscopy findings	IEC (cell/ HPF)	Final status
1	Linear furrows	18	SCS	Linear furrows, concentric rings	20	SCS+SED	-	-	SED
2	White plaque	46	SCS + SED	Concentric rings	52	TCS + SED	Concentric rings	20	SED
3	Normal	20	SCS + TED	Normal	2	TED	-	-	TED
4	Normal	20	SCS	-	-	-	-	-	Cure
5	Erosion	60	SCS	Erosion	0	PPI	-	-	Cure
6	Diffuse ulcer	30	SCS + SED	Less ulcer	20	TCS + SED	-	-	TCS
7	Diffuse ulcer	50	SCS	-	-	-	-	-	Low dose SCS
8	Linear furrows	24	TCS + SED	Linear furrows	4	TED	Normal	0	TED
9	Diffuse ulcer	100	ED	Erosion	7	ED	-	-	Exitus due to sepsis
10	White spots	46	SCS + TED	White spots and fibrosis	32	CS + SED	Normal	0	TED
11	Diffuse ulcer	30	SCS + TED	Normal	5	TED	-	-	Unfollowed
12	Structure	100 and fibrosis	Dilatation + TED + SCS	Linear furrows	81	TCS + SED	Linear furrows	6	TED
13	White spots	60	SCS + SED	Concentric rings	17	SED (bad compliance)	White spots	64	SCS + SED
14	Concentric rings	19	SCS	Hyperemic	1	-	-	-	Cure
15	Diffuse ulcer	36	SCS	-	-	-	-	-	Unfollowed
16	Normal	35	TED	Normal	4	TED	-	-	TED
17	Hyperemic	24	SCS + SED	Hyperemic	0	TED	Normal	45	TCS + SED
18	Concentric rings	35	TCS	Normal	0	-	-	-	Cure

IEC: Intraepithelial eosinophil count, **HPF:** High-power field, **SCS:** Systemic corticosteroid, **SED:** Six-food elimination diet, **TED:** Target elimination diet, **TCS:** Topical corticosteroid.

REFERENCES

1. Liacouras CA, Furuta GT, Hirano I, Atkins D, Attwood SE, Bonis PA, et al. Eosinophilic esophagitis: Updated consensus recommendations for children and adults. J Allergy Clin Immunol 2011;128:3-20.
2. Moawad F. Eosinophilic esophagitis: Incidence and prevalence. Gastrointest Endosc Clin N Am 2018;28:15-25.
3. Chen JW, Kao JY. Eosinophilic esophagitis: Update on management and controversies. BMJ 2017;359:j4482.
4. Leung J, Beukema KR, Shen AH. Allergic mechanisms of eosinophilic esophagitis. Best Pract Res Clin Gastroenterol 2015;29:709-20.
5. Schoepfer AM, Safroneeva E, Bussmann C, Kuchen T, Portmann S, Simon HU. Delay in diagnosis of eosinophilic esophagitis increases risk for stricture formation in a time-dependent manner. Gastroenterology 2013;145:1230-6.
6. Lucendo AJ, Molina-Infante J, Arias A, von Arnim U, Bredenoord AJ, Bussmann C et al. Guidelines on eosinophilic esophagitis: Evidence-based statements and recommendations for diagnosis and management in children and adults. United European Gastroenterol J 2017;5:335-58.
7. Schoepfer A. Diagnostic approach to eosinophilic esophagitis: Pearls and pitfalls. Best Pract Res Clin Gastroenterol 2015;29:783-92.
8. Eluri S, Dellon ES. PPI-responsive esophageal eosinophilia and eosinophilic esophagitis: More similarities than differences. Curr Opin Gastroenterol 2015; 3:309-15.
9. Wittig HJ, Belloit J, De Fillippi I, Royal G. Age-related serum immunoglobulin E levels in healthy subjects and in patients with allergic disease. J Allergy Clin Immunol 1980;66:305-13.
10. Molina-Infante J, van Rhijn BD. Interactions between gastro-esophageal reflux disease and eosinophilic esophagitis. Best Pract Res Clin Gastroenterol 2015;29:749-58.
11. Wen T, Dellon ES, Moawad FJ, Furuta GT, Aceves SS, Rothenberg ME. Transcriptome analysis of proton pump inhibitor responsive esophageal eosinophilia reveals proton pump inhibitor reversible allergic inflammation. J Allergy Clin Immunol 2015;135:187-97.
12. Jiao D, Ishimura N, Maruyama R, Ishikawa N, Nagase M, Oshima N, et al. Similarities and differences among eosinophilic esophagitis, proton-pump inhibitor-responsive esophageal eosinophilia, and reflux esophagitis: Comparisons of clinical, endoscopic, and histopathological findings in Japanese patients. J Gastroenterol 2017;52:203-10.
13. Schoepfer A, Straumann A, Safroneeva E. Pharmacologic treatment of eosinophilic esophagitis: An update. Gastrointest Endosc Clin N Am 2018;28:77-88.
14. Arias A, González-Cervera J, Tenias JM, Lucendo AJ. Efficacy of dietary interventions for inducing histologic remission in patients with eosinophilic esophagitis: A systematic review and meta-analysis. Gastroenterology 2014;146:1639-48.
15. Molina-Infante J, Arias Á, Alcedo J, Garcia-Romero R, Casabona-Frances S, Prieto-Garcia A, et al. Step-up empiric elimination diet for pediatric and adult eosinophilic esophagitis: The 2-4-6 study. J Allergy Clin Immunol 2018;141:1365-72.