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The coexistence of eosinophilic esophagitis with allergic rhinitis

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Abstract. – OBJECTIVE: Eosinophilic esophagitis (EoE) is diagnosed with the presence of characteristic esophageal symptoms and eosinophilic infiltration of the esophageal mucosa after other causes of eosinophilia are excluded. EoE has been reported to co-occur with some allergic diseases. In this study, we evaluated the co-existence of EoE in Ear-Nose-Throat (ENT) outpatient clinic patients with allergic rhinitis (AR).

PATIENTS AND METHODS: The study group consists of 67 AR patients (AR group) and the control group (CG) was formed with 53 cases with dyspepsia symptoms. Symptoms of AR and CG groups were compared in terms of endoscopic and histological findings. Moreover, in AR group, accompanying symptoms, immunoglobulin E (IgE), skin prick test (SPT) positivity, *Helicobacter pylori (H. pylori)* presence, endoscopic findings and biopsy results were compared between patients with EoE and those without.

RESULTS: Seven of the cases with AR were diagnosed with EoE. Reflux symptoms were more common in patients with EoE (71.4%). The presence of *H. pylori* was similar between groups. Blood IgE levels were significantly higher among EoE patients compared to those without EoE ($p = 0.003$). SPT positivity was present in the 85.7% of patients with EoE and 50% of the patients without EoE ($p = 0.113$). Allergens were more likely to be mites *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* in patients with EoE ($p = 0.042$ and $p = 0.034$ respectively).

CONCLUSIONS: The most common symptom among patients with EoE is reflux. In AR patients with EoE, serum IgE levels were higher compared to those without EoE. In AR patients with reflux symptoms, high serum IgE levels, and especially in patients whose tests are positive for allergy to mites, referral to a gastroenterologist for EoE evaluation may be recommended.

Key Words:
Allergic rhinitis, Eosinophilic esophagitis, *Helicobacter pylori*, Immunoglobulin E, Reflux.

Abbreviations

EoE = Eosinophilic esophagitis; AD = allergic disease; SPT = skin prick test; AR = allergic rhinitis; PPI = proton pump inhibitors = CG = control group; IgE = immunoglobulin E; SNOT = sinonasal outcome test; H. pylori = Helicobacter pylori; NCSS = Number Cruncher Statistical System; GERD = gastroesophageal reflux disease.

Introduction

Diagnosed clinicopathologically, eosinophilic esophagitis (EoE) is a notable disease with a recent increase in frequency[1-4]. Eosinophilic infiltration localized to the esophageal mucosa and symptoms vary according to age groups. While refractory reflux treatment, dysphagia and food impaction are the most common symptoms in adults; heartburn, regurgitation, dysphagia, vomiting and abdominal pain are more frequently seen in children[2,4-7].

Clinically, patients with EoE may show chronic esophageal reflux symptoms refractory to treatment, dysphagia, and food impaction as well as allergic manifestations, such as allergic rhinitis (AR), atopic dermatitis and asthma. Similar to other atopic pathologies, its diagnosis has become more common recently due to increased suspicion by clinicians[2,4,8-11]. Allergic diseases (AD), positive skin prick test (SPT), food allergies or aero-allergies is seen in approximately 70% of patients with EoE[3]. Similarly, EoE and AR symptoms may be exacerbated by aero or food allergens[2,12,13].

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In this study, we aimed to determine if there are any foreseeable factors for EoE presence in patients with AR and to evaluate the presence of any predictive factors in these patients. To this end, we compared the symptoms, laboratory findings and presence of allergic conditions in patients with EoE and patients without EoE.

Patients and Methods

Patients

A total of 120 patients were included in the study. The AR group consisted of sixty-seven consecutive patients referred to our Outpatient Clinic from the Ear-Nose-Throat (ENT) Department, with a diagnosis of AR and ate least two years of treatment. The control group (CG) consisted of 53 patients indicated for gastroscopy, which had been evaluated in our Outpatient Clinic due to dyspepsia symptoms. The presence of any malign disease, use of steroid during the last three months and irregular use of PPI for the last two months were exclusion criteria. All the patients had used PPI twice a day regularly during the last two months. Patients with pathologies that would lead to increase in eosinophilic cells[2,14] were not included in either group.

Study Procedure

This non-randomized, single-arm, open-labeled prospective study has been approved by the local research ethics committee. All patients were evaluated for esophageal and gastric symptoms (epigastric pain, dyspepsia, regurgitation, heartburn, food impaction and dysphagia).

Patients' blood immunoglobulin E (IgE) levels were measured and upper gastroscopy was performed. For diagnosis of EoE, biopsies were obtained from the proximal and distal esophagus (3-4 from different locations) as well as the gastric corpus/antrum and duodenum (multiple biopsies). Eosinophilic infiltration was accepted as being positive if, under high magnification, there were≥ 15 eosinophils for patients taking PPI (twice a day/two months) in the esophageal squamous epithelium, and no eosinophils in the gastric or duodenal biopsies under the same magnification[2,15]. After modified Giemsa stain, the presence of *H. pylori* was investigated in the biopsy materials taken from antrum and corpus. In AR group, allergy sino-nasal outcome test (SNOT)[16-18] was performed. SNOT is a questionnaire that measures the health status and quality of life in patients with chronic sinusitis through questions relating to their symptoms[16,18]. SNOT results and presence of major symptoms were noted and SNOT test scores were compared between EoE and non-EoE sub groups of AR.

Symptoms, endoscopic and histological findings between AR and CG were compared. Also, in the AR group, symptoms, IgE levels, SPT positivity, allergy SNOT test results, presence of *H. pylori*, endoscopic and biopsy findings were compared between those with positive for EoE and those negative.

Statistical Analysis

Statistical analysis was performed using the NCSS (Number Cruncher Statistical System) 2007 (Kaysville, UT, USA) program. Apart from descriptive statistics (mean, standard deviation, median, frequency, rate, minimum, maximum), quantitative data was compared using independent groups *t*-test for data with normal distribution and Mann-Whitney U test for data with non-normal distribution; qualitative data was compared using the Pearson Chi-square test and Fisher's exact chi-square test. Statistical significance evaluated for $p < 0.01$ and $p < 0.05$.

Results

Patients' ages ranged from 18 to 67 years. Patients in the AR group were younger than those in CG (33.93 ± 11.29 *vs.* 44.74 ± 13.34, respectively $p < 0.001$). There was no difference for gender between the two groups (females: AR 50, CG 39, $p = 0.897$).

Reflux symptoms, epigastric pain, fullness and bloating symptoms were similar between the two groups ($p > 0.05$). More patients in the AR group were diagnosed with EoE after histopathological evaluation when compared to CG ($p = 0.017$), although there was no difference in the presence of *H. pylori* (AR 61.2% *vs.* CG 49.1%, $p > 0.05$). The results are summarized in Table I.

Evaluation of EoE Cases in AR Group

There was no difference between the average age of male and female patients in the AR group ($p = 0.129$). EoE was diagnosed in 7 patients (10.4%) in this group.

When patients diagnosed with EoE were compared to those without EoE, there was no difference between age, gender, epigastric pain, food

Table I. The overall clinical and demographic profile.

		Control group (n = 53) Mean ± SD	AR group (n = 67) Mean ± SD	p
Age		44.74 ± 13.34	33.93 ± 11.29	[a]< 0.001**
		n (%)	n (%)	
Gender	Male	14 (26.4)	17 (25.4)	[b]0.897
	Female	39 (73.6)	50 (74.6)	
EoE	Yok	53 (100.0)	60 (89.6)	[c]0.017*
	Var	0 (0.0)	7 (10.4)	
Biopsy distal and proximal	Eosinophils ≥ 15hpf	0 (0.0)	7 (10.4)	[c]0.017*
H. pylori	Negative	27 (50.9)	26 (38.8)	[b]0.184
	Positive	26 (49.1)	41 (61.2)	
Symptoms	Dyspepsia	16 (30.2)	13 (19.4)	[b]0.171
	Epigastric pain	16 (30.2)	23 (34.3)	[b]0.631
	Reflux	17 (32.1)	23 (34.3)	[b]0.795
	Dysphagia	0 (0.0)	3 (4.5)	[c]0.254
	No	4 (7.5)	7 (10.4)	[c]0.753

[a]Independent samples *t*-test, [b]Pearson chi-square test; [c]Fisher's exact chi-square test, *$p < 0.05$, **$p < 0.01$.

impaction or dyspepsia symptoms ($p > 0.05$). Reflux symptoms and dysphagia were more frequent in patients diagnosed with EoE (71.4% *vs.* 28.3%, $p = 0.042$ and 28.57% *vs.* 1.67%, $p = 0.027$ respectively).

In patients with EoE, four (57%) had specific EoE endoscopic findings (Figures 1-3), 2 (28.6%) had erosive esophagitis and one had a normal esophageal appearance. In all patients with EoE, proximal esophageal biopsies revealed ≥ 20 eosinophils on high power microscopy. *H. pylori* was positive in 57.1% of patients with EoE diagnosis, and 61.7% of those without EoE diagnosis ($p = 0.999$).

Blood IgE (Normal < 100 IU/ml) was higher in those with EoE diagnosis (281.58 ± 204.12 *vs.* 104.88 ± 190.15, $p = 0.003$) (Figure 4). SPT was positive in 85.7% of patients with EoE and 50% of patients without. There was no difference about allergy test positivity in this group of patients ($p > 0.05$). SNOT test scores were similar between EoE positive and negative patients (57.00 ± 10.76 (56) *vs.* 48.67 ± 12.57 (47), $p = 0.073$). Clinical symptoms (sneezing, coughing,

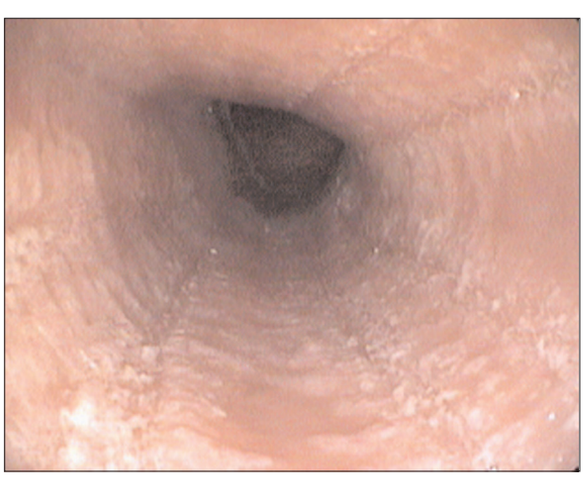

Figure 1. Endoscopic appearance of esophageal mucosa with longitudinal furrowing, mucosal white plaques, loss of capillary markings along the entire length of the esophagus, and mucosal white plaques in the esophagus.

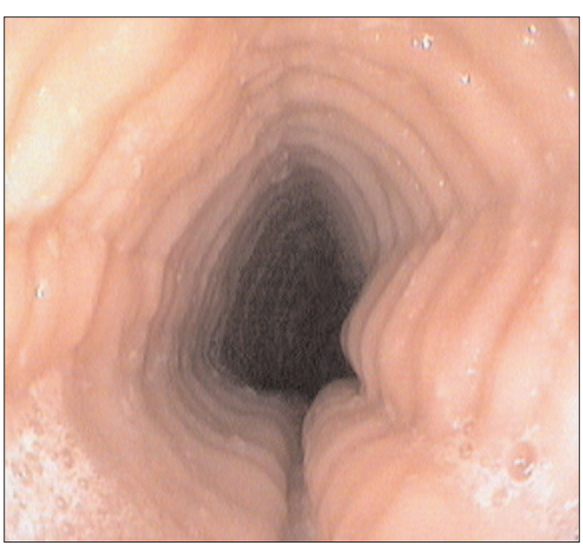

Figure 2. Mucosal rings.

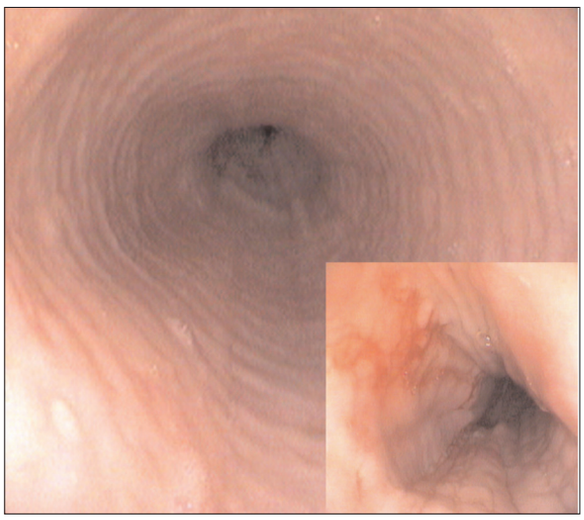

Figure 3. Congestion, crêpe paper, mucosal tears, and decreased vasculature are also present in esophageal lumen of a patient with EoE.

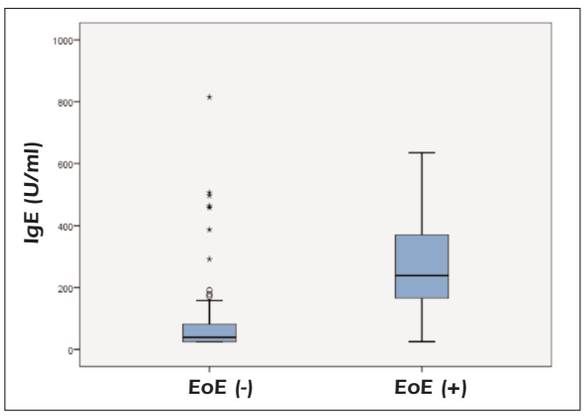

Figure 4. The distributions of IgE levels in between the cases with EoE and without EoE.

running nose, ear pain, etc.) were similar between groups ($p > 0.05$). The results are summarized in Table II.

There was no difference between allergens (grass, trees 1, trees 2, weeds, grass-grains, fungi-a. tenuis, fungi-c. herbarum, sheep wool and rye, $p > 0.05$). Allergens were more likely to be mites *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* in patients with EoE ($p = 0.042$ and $p = 0.034$ respectively) (Table III).

Discussion

The incidence of EoE, which co-exists with atopy, has increased recently with the increase in diagnosis and prevalence of allergic disease[2-4,10]. AR is observed in 10-20% of the general population[19]. Atopy is seen more in patients with EoE when compared to the general population[3,20,21]. Therefore, the structural and emergence properties of atopic patients may help in developing early diagnostic and effective treatment methods for EoE. Early diagnosis and treatment of EoE are also important for the control of symptoms and prevention of complications[6,20,21]. EoE is commonly seen with atopic diseases with diag-

Table II. Results between EoE and non-EoE subgroups of AR.

		EoE (-) (n = 60) Mean ± SD	EoE (+) (n = 7) Mean ± SD	p
Age		39.17 ± 13.50 (38)	31.14 ± 6.96 (32)	[d]0.139
IgE levels		104.88 ± 190.15 (33.5)	281.58 ± 204.2 (239)	[d]0.003**
SNOT test scores		48.67 ± 12.57 (47)	57.00 ± 10.76 (56)	[d]0.073
		n (%)	n (%)	
Gender	Male	15 (25.0)	2 (28.6)	[c]0.999
	Female	45 (75.0)	5 (71.4)	
H. pylori	Negative	23 (38.3)	3 (42.9)	[c]0.999
	Positive	37 (6.7)	4 (57.1)	
Symptoms	Dyspepsia	13 (21.7)	0 (0.0)	[c]0.330
	Epigastric pain	23 (38.3)	0 (0.0)	[c]0.086
	Reflux	18 (30.0)	5 (71.4)	[c]0.042*
	Dysphagia	1 (1.7)	2 (28.6)	[c]0.027*
	No	7 (1.7)	0 (0.0)	[c]0.999

[c]Fisher's exact chi-square test, [d]Mann-Whitney U test, *$p < 0.05$.

Table III. Allergy test and allergen distribution according to presence of EoE.

(n = 67)		EoE (-) (n = 60) n (%)	EoE (+) (n = 7) n (%)	p^c
Allergy test	Negative	30 (50.0)	1 (14.3)	0.113
	Positive	30 (50.0)	6 (85.7)	
Allergens	Herbs	15 (25.0)	3 (42.9)	0.375
	Trees 1	1 (1.7)	0 (0.0)	0.999
	Trees 2	10 (16.7)	1 (14.3)	0.999
	Wild herbs	1 (1.7)	0 (0.0)	0.999
	Herbs-Cereals	9 (15.0)	3 (42.9)	0.103
	Fungi – A. tenuis	0 (0.0)	1 (14.3)	0.104
	Fungi – C. herbarum	1 (1.7)	1 (14.3)	0.199
	Sheep wool	1 (1.7)	0 (0.0)	0.999
	Mite D. Farinae	18 (30.0)	5 (71.4)	0.042*
	Mite D. Pteronyssinus	17 (28.3)	5 (71.4)	0.034*
	Rye	4 (6.7)	1 (1.,3)	0.434

[c]Fisher's exact chi-square test, *$p < 0.05$.

nosis frequently made by gastroenterologists and allergy specialists[2,4]. Our work group consisted of patients with AR, and our research question was "Can EoE be foreseen based on atopic diseases? "

The co-existence of atopic diseases and EoE is common (50-70%)[4,22]. In patients with EoE, incidence of AR, eczema and asthma are reported to be 40-75%, 4-60%, and 14-70% respectively[2,4,10,20-23]. In this study, EoE was diagnosed in 10.44% of patients with AR. In other words, as all patients with EoE also had AR, the atopic disease was present in all of these patients. Despite a low patient number, this can be considered as a striking rate. It is more commonly seen in males (M/F: 2-3/1), its prevalence in adults is reported to be 1/4000 in Sweden and 27/10000 in the USA. Its prevalence is estimated to be 2-6/10000[4,5,11].

On the contrary, gastroesophageal reflux disease (GERD) is commonly seen in males and those younger than 45 years old[2,24]. Despite being more common in males, one study reported a diagnosis of EoE in 2.5% of 311 patients with esophageal symptoms, with 50% of these patients being female[25]. Another report also found the female rate to be higher (M/F: 1/1.5)[26]. The rate of females was also high in our study. This could be considered a factor related to the study group as our patient number is low and the frequency of atopy is higher in females.

Although EoE symptoms are generally gastrointestinal, extra-esophageal symptoms such as cough, wheezing, asthma, pneumonia, globus, hoarseness, AR, sinusitis, atopic dermatitis and eczema may also be observed[2,9,12,27,28]. The significant clinical finding of EoE is the presence of esophageal reflux symptoms refractory to treatment in about 1-4% of the patients[29]. Reflux was reported to be observed in 40% of EoE patients in one study[30]. General symptoms in EoE long-term follow-up are reported as being dysphagia (67.5%), food impaction (80%) and history of atopy (80%)[31]. In a retrospective study[32] of 156 EoE patients, predictive factors for EoE were found to be peripheral eosinophilia, allergic asthma and the presence of AR. Steroid inhalers used for asthma were found to be protective for EoE. From these data, the authors concluded that a scoring system could be developed for predicting the presence of EoE in patients with asthma and difficulty swallowing. In our work, patients with EoE in the AR group were found to have more dysphagia (28.6%) and reflux (71.4%) symptoms when compared to those without EoE in the same group. Dysphagia was observed lesser than expected in EoE patients, and food impaction as not seen in all patients.

The prevalence of EoE in patients with esophageal or upper gastrointestinal symptoms is 6.6%[33]. There are several reports of complex overlapping cases of EoE and GERD. EoE should be considered when reflux symptoms are refractory to treatment[20,34]. The most frequently seen symptom in patients diagnosed with EoE having different esophageal symptoms and with the patients having various allergy symptoms was reported as heartburn[25]. It is known that 70% of EoE patients with co-existing reflux were previously misdiagnosed as GERD[27]. In our study,

the most common symptom in patients with AR and EoE was reflux. Similar to our research, Dellon et al[27] and Joo et al [33] observed reflux symptoms in 70% and 61.5% of patients, respectively.The high rate of reflux symptoms in our EoE patients is expected. This high rate of reflux symptoms in patients with AR, may suggest an association of allergic origins and EoE. In EoE patients, AR was seen in 37.5%, GERD in 62.5% and atopic dermatitis in 25% of patients, a higher rate than patients without EoE. The same study reported a high incidence of epigastric pain, reported to occur in 61.5% of patients[33]. In our paper, epigastric pain, bloating and feeling of satiety was similar in patients with EoE and those without (Table II).

The endoscopic evaluation of EoE cases demonstrated a relatively high diagnostic value for linear furrows and ring-like appearance[33]. While these are characteristic findings in EoE, up to a third of patients may have a normal appearing esophagus[1,4]. Endoscopic evaluation of 19 patients with EoE revealed a normal esophagus in 7 patients[35]. When patients diagnosed with EoE in our study are evaluated, four (57%) had specific endoscopic EoE findings, two (28.6%) had erosive esophagitis and one patient had a normal appearing esophagus.

There are conflicting results from studies evaluating the relationship between EoE and *H. pylori*. Some limited studies have reported a lower infection rate of *H. pylori* in EoE patients when compared to the normal population[11,36]. In contrast, a study of Asian EoE patients reported a high co-existence of *H. pylori* in eosinophilic gastrointestinal pathologies[37,38]. Data obtained from observational publications have demonstrated a weak inverse relationship between *H. pylori* infection and the prevalence of allergy[39]. While there is insufficient data in adults, a study of children in West Virginia found an inverse relationship between *H. pylori* and EoE[40]. Here, we found no difference regarding the presence of *H. pylori* between AR and CG groups or between those diagnosed with EoE and those not, in the AR group ($p = 0.816$).

Although there are no known diagnostic serum markers for EoE, IgE levels are reported to be > 114,000units/L in 50-60% of patients and mild increase of peripheral eosinophils are also reported in 40-50% of patients. Allergic and immunological evaluation using allergy tests may be useful in diagnosing atopic patients. AR is also a IgE dependent disease[2,9,12,14,41]. Thus the limited role of serum IgE levels is consistent with consensus recommendations for children and adults[23]. In our AR group, serum IgE levels were higher in patients diagnosed with EoE compared to those not diagnosed ($p = 0.003$). It was especially striking that in the allergic patients group, IgE levels were 2.7 times higher in patients diagnosed with EoE when compared to those without EoE.

SPT is an allergy test used for food and aero allergies. SPT reflects IgE-mediated allergic reactions to antigens[14]. Patients with EoE, increased IgE and SPT positivity is reported in 40-73% of patients[2, 3]. We also found a very high (85.7%) SPT positivity in our EoE patients. In addition, mildly high SPT positivity, according to literature, may be explained by the fact that our EoE patients could also be AR patients with aeroallergens in the foreplan. Also, a separate study reported that 27-47% of EoE patients may be SPT negative, and that non-allergen endogenous mechanisms independent of IgE may play a role in such cases[42].

Apart from allergy tests, symptoms of atopic diseases such as AR, atopic dermatitis, and asthma may accompany EoE[4,22]. It has been reported that the presence of asthma or food allergies is a clear risk factor for EoE[43]. Nasal symptoms and rhinosinusitis have been reported in 19-25% of children with EoE[9]. In our study, we used the SNOT test to determine if the presence of EoE had an effect on the severity of AR symptoms. However, we found no difference in SNOT tests scores in those diagnosed with EoE and those not diagnosed. There was also no difference between these groups concerning pronounced symptoms, such as running nose, sneezing, ear ache or coughing, etc.

The prevalence of atopic diseases such as environmental or food allergies is 50% higher in adults and children with EoE when compared to the general population[20,21,41]. The removal of allergic foods is known to be 70% effective in the treatment of EoE. Therefore, SPT and patch tests are used in patients with EoE for the diagnosis of food allergies, and to improve outcome[12]. While SPT and serum specific IgE test have similar diagnostic characteristics, SPT is generally considered to be more sensitive[44-46]. In adults with EoE, 80.9% were reported to be sensitive to multiple environmental allergens and 82.6% had positive serum specific IgE for at least one food type[21]. The clinical evaluation of allergic status is suggested for the management of patients with EoE.

It has also been reported that the presence of atopy is predictive for less response to treatment in EoE[15,23,47,48]. We also evaluated the allergy status in the AR group using SPT and found that mites *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* were more common in those diagnosed with EoE (Table III). A reported pediatric patient related with this subject was confirmed to have an allergy against the same mites tested postitive as our EoE patients have. This patient was required to have immunotherapy to cure the illness successfully. It has been demonstrated that SPT activity becomes negative after treatment[48].

Limitations of our report were the small number of patients in the AR group, which was predominantly made up of females. It was noted that AR patients presenting to ENT outpatient clinic were also predominantly females. A reflux symptom score may also have been performed in the AR group, before and after PPI usage. This would have been useful to compare the symptoms of patients with and without EoE.

Conclusions

The co-existence of EoE in AR is substantially noteworthy. As reflux was the most commonly seen symptom in our study, we believe the evaluation for EoE should not be ignored when atopic diseases are present. Also, it should not be forgotten that patients with EoE may present with atopy or allergic diseases. There was no increase in AR symptoms in patients we diagnosed with EoE. However, serum IgE was higher when AR and EoE co-existed when compared to AR patients without EoE. In AR patients with high serum IgE levels and allergy test positivity against mites, EoE should be evaluated by inquiry of symptoms such as reflux and dysphagia, especially if corticosteroid or immunosuppressive treatment is to be started. Questioning of these symptoms will help with diagnosis and allow for earlier and more successful treatment. The common co-occurence of EoE and AR requires the collaboration of different specialties, especially ENT, allergists and gastroenterologists.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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