Prevalence of Eosinophilic Esophagitis in Patients with Dysphagia in the Turkish Population

Türk Popülasyonunda Disfaji ile Başvuran Hastalarda Eozinofilik Özofajit Sıklığı

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ABSTRACT Objective: In this study we aimed to investigate the prevalence of eosinophilic esophagitis (EoE) among patients with dysphagia in the Turkish population. **Material and Methods:** Patients with dysphagia were enrolled in the study. The enrolled patients underwent esophagogastroduodenoscopy and esophageal biopsies were obtained-one from proximal and one from mid-esophagus. Esophageal motor disorders (EMD) which can cause dysphagia (achalasia etc) were excluded by esophagial manometry. The diagnosis of EoE was made when patients had chronic esophageal symptoms and the esophageal biopsy showed >15 eosinophils/high-power field (HPF). **Results:** A total of 107 patients with dysphagia were enrolled in the study. After exclusion of patients with EMD and other structural or systemic diseases, 55 patients were left in the study. Ten of 55 patients (18.2%) were male and the median age of patients was 45 (18-80) years. All patients had dysphagia. Overall 37 (67.3%) had regurgitation, 35 (63.6%) pyrosis, 9 (16.4%) epigastric pain, 17 (30.9%) nausea and one patient (1.8%) had vomiting. In the initial routine histopathological examination, five patients reported to have eosinophilic esophagitis but re-evaluation of histopathological findings revealed that only one patient met the diagnostic criteria for Eosinophilic Esophagitis (EoE). However, gastric biopsy of this patient showed intense eosinophilic infiltration and the diagnosis of eosinophilic gastroenteritis was more likely in that patient. **Conclusion:** As a result, despite the small number of patients, eosinophilic esophagitis is suggested to be one of the least common causes of dysphagia among adult patients in the Turkish population.

Key Words: Eosinophilic esophagitis; deglutition disorders

ÖZET Amaç: Bu çalışma, disfaji nedeniyle başvuran Türk hastalarda eozinofilik özofajit sıklığını araştırmak amacıyla planlanmıştır. **Gereç ve Yöntemler:** Çalışmaya disfajisi olan hastalar alındı. Çalışmaya alınan hastalara özofagogastroduodenoskopi yapıldı. Özofagus orta ve proksimalinden birer biyopsi alındı. Disfajiye neden olabilecek özofagus motor fonksiyon bozuklukları özofagiyal manometri ile dışlandı. Eozinofilik özofajit tanısı, disfajisi olan hastaların biyopsilerinde bir büyük büyütme alanında >15 eozinofil olması ile konuldu. **Bulgular:** Çalışmaya toplam 107 hasta alındı. Dışlama kriterlerine göre motor fonksiyon bozukluğu ve diğerleri çıkarıldıktan sonra 55 hasta kaldı. Elli beş hastanın 10 (%18,2)'u erkek olup, ortanca yaş 45 (18-80) idi. Bütün hastalarda disfaji vardı. Hastaların 37 (%67,3)'sinde regürjitasyon, 35 (%63,6)'inde pirozis, 9 (%16,4)'unda epigastrik ağrı, 17 (%30,9)'sinde bulantı ve 1 (%1,8)'inde kusma saptandı. İlk rutin histopatolojik incelemede 5 hastada eozinofilik özofajit olduğu raporlandı; fakat eozinofilik özofajit kriterlerine göre tekrar değerlendirildiğinde 1 hasta kriterlere uygun bulundu. Ancak bu hastanın gastrik biyopsisinde yoğun eozinofil infiltrasyonu olması nedeniyle eozinofilik gastroenterit tanısı daha uygundu. **Sonuç:** Bulgularımız, hasta sayımızın az olmasına rağmen Türk toplumunda eozinofilik özofajite bağlı disfajinin sık olmadığını göstermektedir.

Anahtar Kelimeler: Eozinofilik özofajit; yutma bozuklukları

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Eosinophilic esophagitis (EoE) is a disorder characterized by an abnormal accumulation of eosinophils in the esophageal mucosa and is associated with symptoms of dysphagia and esophageal food impaction.[1] Diagnosis depends on the histopathological finding of mucosal eosinophilia. According to the current guideline recommendations, 15 or more eosinophils per high power field (HPF) on hematoxylin and eosin (H&E) stain in at least one biopsy are adequate for diagnosis in the appropriate clinical setting.[1] There are increasing prevalence and incidence rates of EoE in both children and adults in the literature.[2,3]

The most frequent manifestations of EoE in adults are dysphagia, food impaction and chest pain. Heartburn may also present and require a differential diagnosis from gastroesophageal reflux disease (GERD).[4]

Several studies reported a wide range of EoE prevalence according to the study population and eosinophil cut-off value. Although the prevalence of EoE among European adults was reported as 0.4% the percentage of patients with typical EoE symptoms such as dysphagia, food bolus obstruction or refractory gastroesophageal reflux disease (GERD) varied from 8.8% to 33%.[5-7] A Korean study investigating the prevalence of EoE among patients with dysphagia or reflux-related symptoms yielded a rate of 6.6%.[8] A report from Ireland shows that the prevalence of eosinophilic esophagitis is only 0.1% in a large group of patients.[9] There is controversy among studies reporting the prevalence of EoE among patients with various esophageal symptoms. This is important because EoE patients may suffer from a range of symptoms in addition to dysphagia and food impaction.

In this study, we aimed to investigate the prevalence of EoE among patients who had dysphagia and to determine the endoscopic, symptomatic and histopathological features of EoE patients in the Turkish population.

MATERIAL AND METHODS

PATIENTS

In this study, patients aged between 18-80 years with dysphagia who visited the Gazi University Faculty of Medicine Department of Gastroenterology to undergo esophagogastroduednonoscopy (EGD) from June 2010 to July 2011 were recruited. Esophageal motor functions disorders like achalasia were excluded by high-resolution esophagial manometry with impedance using water-perfused manometry catheter with impedance. Ten wet swallows with salty water were performed during esophageal manometry. The other exclusion criteria were the presence of diabetes mellitus (DM), scleroderma, skin disorders, which can affect the esophagus like lichen planus, all of which could cause dysmotility in the esophagus and the presence of malignant or benign stricture in endoscopy. Endoscopic biopsy was obtained from proximal-mid region of the esophagus in order to exclude the eosinophilia due to gastroesophageal reflux disease (GERD). This study was approved by the Local Ethical Committee.

HISTOPATHOLOGY

Esophageal biopsies were obtained from the proximal-mid region regardless of endoscopic findings. Gastric biopsies were also obtained at least from two different sites in all cases. The esophageal mucosal biopsy specimens were transferred separately into formalin by the Department of Pathology of Gazi University Faculty of Medicine. After hematoxylin and eosin (HE) staining, the specimens were examined by experienced, blinded gastrointestinal pathologists. The cut-off value of the eosinophil count was set as the presence of ≥15 eosinophils/HPF on either middle or proximal esophageal biopsy specimen. The pathologists also noted other findings that could be additional histological features associated with EoE, such as eosinophilic micro abscess, superficial layer of eosinophils or basal zone hyperplasia.[10] Histopathologically suited cases (eosinophil ≥15/HPF) were not considered as EoE if they had at the same time erosive esophagitis with definite mucosal break (s), eosinophilic gastroenteritis.

Considering the clinical, endoscopic and histopathologic informations, EoE was diagnosed if the patient had esophageal symptoms (dysphagia, food impaction, acid regurgitation, heartburn, chest pain nausea and/or vomiting and epigastric

pain) with the proven histological finding of ≥15 eosinophils/HPF and was unresponsive to 2-4 weeks of proton pump inhibitor (PPI) therapy.

STATISTICAL ANALYSIS

Statistical analyses were conducted using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were performed for continuous variables as mean±standart deviation or as median (min-max). For expressing variables, number of cases and % were used.

RESULTS

One hundred and seven patients with dysphagia who presented to the Gastroenterology Department of our hospital between June 2010 and July 2011 were enrolled in the study. Patients who had esophageal motor disorder, scleroderma, carcinoma, mass lesions, distal strictures secondary to gastroesophageal reflux disease and other findings, which may cause dysphagia were excluded except for patients with endoscopic findings of eosinophilic esophagitis (feline esophagus, linear furrows, whitish papules, strictures, small caliber esophagus etc.). Fifty-five patients fulfilled the inclusion criteria and data were analyzed for these patients. Ten out of fifty-five patients (18.2%) were male and the median age was 45 (18-80) years.

All patients had dysphagia. In the study group, 37 (67.3%) patients had regurgitation, 35 (63.6%) had pyrosis, 9 (16.4%) had epigastric pain, 17 (30.9%) had nausea and one patient (1.8%) had vomiting (Table 1). Thirty patients (54.5%) had dysphagia longer than 12 months. Twenty-eight (50.9%) patients had dysphagia against solid foods, 5 (9.1%) against liquid and 22 (40%) against both forms as shown in Table 2.

Regarding the allergy status of the patients 1(1.8%) had pollen allergy, 4 (7.2%) had house dust allergy and 1 (1.8%) had food allergy. In addition, 2 (3.6%) patients had allergic rhinitis and 2 (3.6%) had asthma but none of the patients had atopic dermatitis.

According to the endoscopic appearance, 50 (90.9%) patients had normal esophagus, 3 (5.5%) had reflux esophagitis and two (3.6%) had short segment Barrett's Esophagus as shown in Table 3.

TABLE 1: The distribution of patients according to the symptoms.

Symptom	Pateints (n)	The percentage of patients(%)
Dysphagia	55	100
Regurgitation	37	67.3
Pyrosis	35	63.6
Epigastric pain	9	16.4
Nausea	17	30.9
Vomiting	1	1.8

TABLE 2: Distribution of patients according to the duration and character of dysphagia.

		Patients n (%)
Character of dysphagia	Solid	28 (50.9%)
	Liquid	5 (9.1%)
	Both	22 (40%)
	Total	55 (100%)
Duration of dysphagia	0-6 months	19 (34.5%)
	6-12 months	6 (11%)
	>12 months	30 (54.5%)
	Total	55 (100%)

Five patients had esophagial eosinophilia. The highest numbers of eosinophilia in a magnified field in those patients were 1, 2, 4, 7 and 85 respectively. Three of these patients were female. The median age was 47 (18-62). In two patients, the duration of dysphagia was shorter than 6 months; the remainder had dysphagia longer than 12 months. Three patients had dysphagia against solid foods and two patients had dysphagia against both solid and liquid foods.

Two patients had peripheral eosinophilia and their eosinophil numbers were 500/mm^3 and 690/mm^3. The patients who had esophagial eosinophilia also had higher peripheral eosinophil numbers.

Five patients with esophageal eosinophilia had normal appearance in EGD. Esophageal manometry was performed and two of patients had hy-

TABLE 3: Distribution of patients according to the endoscopic findings of esophagus.

Endoscopic findings of esophagus	Patients (n)	The percentage of patients (%)
Normal	50	90.9
Reflux Esophagitis	3	5.5
Barret's Esophagus	2	3.6
Total	55	100

potensive Lower Esophageal Sphincter (LES), one patient had hiatal hernia and the remaining two had normal findings. The clinical features of patients with esophageal eosinophilia were shown in Table 4**.** Histopathological findings of patients with esophageal eosinophilia were shown in Table 5**.**

As a result, 54 out of 55 patients with dysphagia enrolled in our study did not meet the criteria of histopathological diagnosis. One patient met the criteria of eosinophilic esophagitis but the presence of intense infiltration of eosinophils in the stomach biopsy made eosinophilic gastroenteritis more likely.

DISCUSSION

The thorough investigation of 55 patients (total 107) in our study with dysphagia and without any other diagnosis did not reveal eosinophilic esophagitis. Considering the baseline characteristics and past history, patients with EoE had suffered from GERD, allergic rhinitis or house dust allergy. These results are not surprising because the pathogenesis of this disease is associated with aeroallergens or skin sensitization.[11]

From an endoscopic point of view, 5/55 (9%) of all patients with various esophageal symptoms or with dysphagia or refractory GERD had endoscopic features suggesting EoE in our study. However, the histopathological examination revealed no EoE diagnosis, which was interpreted as EoE being uncommon in the Turkish population although the study included a small numbers of patients. We may suggest that this entity is not as common as reported in different populations.[12]

Considering their histopathological characteristics, 5 patients had eosinophilic infiltration at both the middle and proximal esophagus. According to routine histopathological evaluation of patients, eosinophilic esophagitis was detected in 2 patients, normal esophageal biopsy in 2 patients and reflux esophagitis in 1 patient. All biopsies were re-evaluated according to internationally recognized criteria and only one patient had an eosinophil count meeting the diagnostic criteria of EoE. The biopsy of the patient with 85 eosinophils per magnification field included histopathological findings such as basal cell hyperplasia, degranulating eosinophils, papillary elongation and necrotic epithelial cells. Eosinophils were located on both the superficial

TABLE 4: The features of patients with esophageal esonophilia.

Patient features	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age	48	62	54	18	56
Gender	F	F	M	F	F
PPI use	No	No	No	No	Yes (>8week)
The presence of allergy	No	No	No	No	No
The presence of asthma	No	No	No	No	No
Family history of allergy	No	No	No	No	No
Family history of asthma	Yes	No	No	No	No
The presence of peripheral eosinophilia	Yes	Yes	No	No	No
Peripheral eosinophil count/mm^3	690	500	0	0	100
Results of esophageal manometry	Hypotensive LES	Hiatal hernia	Hypotensive LES	Normal	Normal

F: Female; LES: Lower esophageal sphincter; M: Male; PPI: Proton pump inhibitor.

TABLE 5: Histopathological findings of patients with esophageal eosinophilia.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
The first histopathological diagnosis	EoE	Normal	Reflux esophagitis	Normal	EoE
Eosinophil count / hpf	85	1	7	2	4
Localization of eosinophils	Superficial+basal	Basal	Basal	Basal	Superficial+basal
Degranulating eosinophil count	15	0	2	2	0
The presence of micro-abscess	Yes	No	No	No	No
The presence of necrotic epithelium	Yes	No	No	No	No
Basal cell hyperplasia	Yes (60%)	No	No	No	No
Expansion of the intercellular space	No	No	No	No	No
Papillary elongation	Yes	No	No	No	Yes
Fibrosis of the lamina propria	No	No	No	No	No
Intraepithelial lymphocyte count/Hpf	10	2	12	14	10
Gastric biopsy	Eosinophilic gastritis	Chronic gastritis	Normal	Chronic gastritis	Normal
The presence of *H.pylori*	No	No	No	No	No
New histopathological diagnosis	Eosinophilic gastritis	Reflux esophagitis	Reflux esophagitis	Reflux esophagitis	Reflux esophagitis

EoE: Eosinophilic esophagitis; Hpf: High power field.

and the basal layers of the epithelium. Although histopathologic evaluation was compatible with eosinophilic esophagitis, the biopsy of gastric antrum of the patient had intensive eosinophil infiltration (>150/eosinophil/HPF) and the patient was diagnosed with eosinophilic gastritis. The remaining 4 patients with esophageal eosinophilia according to the current histopathological findings were diagnosed with reflux esophagitis.

In other studies with a high prevalence for EoE, major motility disorders that could cause dysphagia were not excluded by motility studies and biopsy form any area of the esophagus might affect the results of the studies. The major difference of our study compared to others was the exclusion of the most important differential diagnosis of EoE such as reflux esophagitis and esophageal motility disorders. To exclude eosinophilia, which might be associated with gastroesophageal disease (GERD), the patients whose esophageal biopsies were obtianed from the middle and the proximal regions were enrolled in the study.[4,13,14] Although eosinophilia due to gastroeosephageal reflux disease is usually present in the distal esophagus, eosinophilia of eosinophilic esophagitis can be seen in the any part of the esophagus.[4] Liacouras et al. determined 100% sensitivity when they compared mid-esophageal biopsy with distal esophageal biopsy in the diagnosis of the EoE.[15]

There are several limitations of our study. We did not perform biopsy from all parts of the esophagus; only the middle and proximal parts of the esophagus were biopsied once; due to the patchy involvement pattern of EoE, just one biopsy specimen from each part might be insufficient to make a diagnosis of EoE.

In conclusion, despite the small number of cases, eosinophilic esophagitis may be among the uncommon causes of dysphagia among adult patients in Turkey.

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