

Eosinophilic Esophagitis in Patients with Refractory Gastroesophageal Reflux Disease

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Abstract *Background* Eosinophilic esophagitis is among the causes of refractory reflux disease. Biopsy of esophagus is the gold standard for diagnosis. In this study we determined the frequency of eosinophilic esophagitis (EE) in refractory reflux cases referred to Motility Department of Shahid Beheshti Research Center of Gastroenterology and Liver Disease, Tehran, Iran. *Methods* In this cross-sectional study, 68 cases with refractory reflux disease underwent endoscopy and had biopsies taken. Specimens were stained by hematoxylin and eosin and two independent pathologists confirmed the diagnosis of eosinophilic esophagitis. *Results* Mean (standard deviation, SD) age at diagnosis was

41.8 (10.94) years. All had allergy or atopy, and unknown dysphagia was noted for 66%. Endoscopic findings were as follows: esophagitis (33.3%), rings (33.3%), and whitish plaques (33.3%). Prevalence of eosinophilic esophagitis was 8.8% ($N = 6$; one man and five women). No statistical difference in demographic variables was found between eosinophilic esophagitis cases and others, except for history of atopy, food impaction, and endoscopic features (P value <0.005). *Conclusion* Eosinophilic esophagitis should be considered in the differential diagnosis of any cases with refractory reflux who complain of chronic unexplained dysphagia, with history of recurrent food impaction, and atopy or abnormal endoscopic features.

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Introduction

Reflux is one of the most common causes of physician visits. A subgroup of patients with reflux continue to be symptomatic when treated with proton pump inhibitors and are considered refractory gastroesophageal reflux cases. One etiology mentioned for refractory reflux is eosinophilic esophagitis (EE), which is rapidly emerging as a distinct disease entity [1]. EE can be defined as remarkable infiltration of eosinophils in the epithelium of esophagus of more than 20 eosinophils per high-power field (HPF) on microscopic examination [1, 2].

Nowadays EE is diagnosed more and its prevalence was reported to be 68–94% in children with refractory reflux [2, 3]. Its prevalence has not yet been determined in adults. It was reported in 19 persons of an Australian population of 198,000, during a period of 21 months [4].

A typical case of EE is a young man with an atopic background who presents with solid-food dysphagia. In these cases endoscopic procedure is commonly performed due to food impaction.

Eosinophilic esophagitis should be suspected, particularly in patients with unexplained dysphagia or those with no response to antacid or anti-acid secretory therapy [1].

Food impaction and esophageal strictures and perforation, and negative impacts on social activities, can result from misdiagnosis [1].

This disease is not efficiently evaluated in refractory reflux cases in Iran and other countries, because gastroenterologists did not know that EE can occur in mucosa with healthy appearance, thus selection bias can occur. Also, no clear definition is available [5].

This study was designed to evaluate the frequency of eosinophilic esophagitis in adult cases with refractory reflux referred to Motility Department of Shahid Beheshti Research Center of Gastroenterology and Liver Disease and Taleghani Hospital, Iran, 2006.

Materials and Methods

This cross-sectional study was done on adults with refractory reflux disease referred to Imam Hossein and Taleghani hospital, Tehran, 2006. Cases were determined by upper gastrointestinal tract symptom severity index (PAGI-SYM) [6], and were enrolled into the study if no response was reported to omeprazole 20 mg/day for at least 8 weeks. Symptoms were as follows: heartburn in supine or upright position, regurgitation, noncardiac chest pain, and food impaction. A questionnaire was completed for each person. Exclusion criteria were as follows: (1) corticosteroids or immunosuppressive agents consumption during the past 3 months, (2) Barrett’s esophagus, (3) parasitic or fungal infection, (4) carcinoma, (5) Crohn’s disease, and (6) collagen vascular diseases.

All cases underwent upper endoscopy by a gastroenterologist, who was the leader of the research group, with Olympus Endoscope, Evis Exera, and after reporting the observation, several biopsies were taken from 2–4 cm and 8–10 cm from lower esophageal sphincter (LES), and also samples were taken from every visible lesion.

Samples were transferred separately into formalin regards to the site of biopsy, to the Pathology Department of Taleghani Hospital (Gastrointestinal Research Center). After hematoxylin and eosin staining, samples were observed by two independent pathologists. Cases with more than 15 eosinophils in squamous epithelium of their esophagus per HPF or eosinophilic microabscess (aggregation of 3–4 eosinophils) were diagnosed as eosinophilic esophagitis [1, 2].

Sixty-eight cases were eligible to be enrolled. Data were coded and analyzed with SPSS software; Pearson chi-square and Fisher’s exact test were used.

Results

Mean (±SD) age of the cases was 41.29 (±3.33) years. Reflux symptoms persisted for a mean of 50.5 ± 4.85 months (*P* > 0.05).

Twenty-eight were males (41.17%) and 58.82% were females. Eosinophilic esophagitis was diagnosed in six patients (8.8%) (male-to-female ratio 1:5).

No significant differences were seen between EE cases and other patients with regards to age or sex (*P* > 0.05).

Among these 68 cases, 16 (23.5%) had history of atopy. Difference of this variable was significant between EE cases and others (*P* < 0.001). The exact frequency of each type of atopy in the EE and non-EE group is presented in Table 1.

As shown in Table 2 endoscopic presentations were significantly different between EE cases and others (*P* < 0.001) (Table 2).

Table 1 Frequency of each type of atopy in the study population

Atopy	Pathology		Total	<i>P</i> value
	Eosinophilic esophagitis, <i>n</i> (%)	Other pathologic changes, <i>n</i> (%)		
Atopy	6 (100)*	10 (16.2)*	16	<0.001
Asthma	1 (16.6)	1 (1.62)	2	NS
Urticaria	2 (33.3)	3 (4.83)	5	NS
Atopic dermatitis	0 (0.00)	1 (1.62)	1	NS
Rhinoconjunctivitis	3 (50)	3 (4.83)	6	NS
Food allergy	0 (0.00)	1 (1.62)	1	NS
Others	0 (0.00)	1 (1.62)	1	NS
<i>N</i>	6	62	68	–

* *P* < 0.05 significant

Table 2 Esophageal endoscopic findings in cases diagnosed as eosinophilic esophagitis and other patients presenting with refractory reflux

Endoscopic features	Histopathologic report		Total	P value
	Eosinophilic esophagitis (N)	Other pathologic changes (N)		
Esophagitis	2	30	32	<0.000
Corrugation	0	1	1	NS
Rings	2	0	2	NS
Whitish plaques	2	5	7	NS
Small caliber	0	1	1	NS
Normal	0	22	22	<0.000
Others	0	3	3	NS
Total	6	62	68	–

Table 3 Food impaction during a week and histopathologic changes in patients presenting with refractory reflux

Food impaction	Histopathologic report		Total	P value
	Eosinophilic esophagitis (N)	Other pathologic changes (N)		
Not at all	2	57	59	<0.000
One day per week	0	2	2	NS
2–4 days per week	3	1	4	NS
Almost every day	1	2	3	NS
Total	6	62	68	–

Food impaction was seen significantly more in EE ($P < 0.001$) (Table 3).

Pyrosis was mentioned by all EE cases for more than 2–4 days per week ($P > 0.05$).

Frequency of heartburn in supine position and regurgitation were significantly different between EE patients and others, but not in upright position.

Another symptom was noncardiac chest pain, which was not significantly different between the two groups ($P > 0.05$).

Dosage and duration of omeprazole consumption were not significantly different between the two groups (Table 4).

Cigarette smoking and alcohol consumption were very rare in both groups.

Table 4 Duration of proton pump inhibitor consumption and histopathologic changes seen in endoscopic survey of refractory reflux cases

Times	Histopathologic report		Total
	Eosinophilic esophagitis	Other pathologic changes	
0–36 months	1	2	3
37–192 months	5	60	65
Total	6	62	68

Discussion

Eosinophilic esophagitis is one of the reasons considered for refractory reflux, which is increasing in prevalence [1]. Misdiagnosis can result in negative effects on social behaviors; food impaction and perforation of the esophagus are the two main complications of EE [1].

Other studies showed a mean age of 23–44 years in EE patients [1, 7]. This result was seen in our study, too (mean 41.8 years).

In contrast to other observations [1, 4, 7, 8], EE was seen more in women (86.6%) of our area. The environment or surveying refractory cases may play a role in this difference, because other investigations were done in a population with reflux, not only refractory reflux cases.

In this study, atopy was seen in all EE cases and the differences between EE and other patients were significant. This was lower in other studies [8, 9] and can indicate higher incidence of atopy in our area. Environmental factors may have a more predominant role in our area.

The most common symptoms in other studies were as follows: long-lasting dysphagia, esophageal food impaction, symptoms of gastroesophageal reflux disease (GERD), and pyrosis [8–10]. The most common symptoms of the present study were as follows: pyrosis, heartburn in supine mode, regurgitation, heartburn in upright position, noncardiac chest pain, and food impaction.

These may suggest that food impaction necessitates performance of endoscopy.

Subtle endoscopic findings, such as “feline” or corrugated esophagus with fine rings, diffusely narrowed esophagus with probable proximal strictures, linear furrows, adherent white plaques, or friable (crepe paper) mucosa, prone to tearing with minimal irritation, can be simply neglected. A histologic examination must be done, although no pathologic consequences have been established [8, 11].

Duration of symptoms and history of taking medicines were not related to results of histopathologic examination, esophageal pathology or other variables.

Long-term prognosis of EE is not defined certainly; but it is assumed to be a benign process. The role of EE in differential diagnosis of solid-food dysphagia will be prominent, while our recognition of the entity is increasing [11].

Conclusions

Although the numbers of EE cases in our study were very low and more comprehensive studies are needed, it can be suggested that, in patients with history of atopy and symptoms such as food impaction, this diagnosis can be considered as an important entity.

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