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Clinical presentation and endoscopic findings in adult patients with eosinophilic esophagitis

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Ethics Committee Approval
The study protocol was approved by Acibadem Mehmet Ali Aydinlar University Evaluation Committee for Medical Research (ATADEK), (no: 2022-14/5; date: September 2, 2022). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: The frequency of eosinophilic esophagitis has been rising over the last decades. It is diagnosed primarily based on symptoms and endoscopic and histopathological examination findings. Although eosinophilic esophagitis is not associated with malignancy, it remains an important condition affecting both children and adults, as it is associated with morbidity such as dysphagia, food impaction, and esophageal strictures. This study aimed to define clinical and endoscopic characteristics of adult patients diagnosed with eosinophilic esophagitis based on recently recommended histopathological criteria.

Methods: This retrospective cross-sectional descriptive study included 54 adult patients (mean age: 33.6 yr, range: 16–61 yr) who underwent upper gastrointestinal system endoscopy for dyspeptic complaints (epigastric pain, reflux, dysphagia, or food impaction) and diagnosed with eosinophilic esophagitis based on the latest histopathological criteria (≥15 eosinophils per high-power field). Patients with a history of malignancy were excluded. Patients' clinical, endoscopic, and histopathological data were examined.

Results: In patients diagnosed with eosinophilic esophagitis, the most common presenting complaint was dysphagia (61.1%), followed by dyspepsia (24.0%), regurgitation (16.6%), chest pain (16.6%), epigastric pain (12.9%), food impaction (11.1%), and halitosis (3.7%), without any age predilection for the complaints. White papules and linear furrow were the most frequent findings on endoscopic examination (35.1% each), followed by circular rings (24.0%), paleness (22.2%), normal endoscopic finding (20.3%), and small-caliber esophagus (11.1%).

Conclusion: The diagnosis of eosinophilic esophagitis remains challenging due to considerable variations in definitions and in the relative frequencies of endoscopic findings. Therefore, we recommend combining clinical, endoscopic, and histologic criteria to establish diagnosis. The identification of standards for diagnosis in future studies is warranted.

Keywords: Eosinophilic esophagitis, Endoscopic examination, Histopathological examination, Eosinophil count

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Introduction

Eosinophilic esophagitis (EoE) is a relatively rare entity first reported in 1978 by Landres et al. [1]. It is characterized by a dense infiltration of eosinophils in esophageal mucosa without similar findings in the stomach or duodenum and is associated with esophageal symptoms [2]. Although a precise etiology remains unknown, its high coincidence with atopic diseases, including atopic dermatitis, asthma, and allergic rhinitis, suggests an allergic background [3-6].

Despite initial sporadic reports, the frequency of eosinophilic esophagitis seems to rise over decades [7]. A Swedish study reported a more than 10-fold rise in its prevalence between 1989 and 2004 [8]. Similarly, a US study reported an increase to 55 per 100,000 population prevalence over the last three decades [9]. Another study showed a 6.5% prevalence among individuals who underwent endoscopy examination [10], highlighting the importance of the condition from a public health standpoint. A recent meta-analysis found that the incidence rate was 6.6/100,000 person-years in children, and 7.7/100,000 person-years in adults, and that the prevalence was 34 cases per 100,000 children and 42.2 cases per 100,000 adults [11].

It is more common in men, with a male to female ratio of 3:1, and there is a peak in the third to fifth decades of life [12].

Diagnosis of eosinophilic esophagitis is primarily based on esophageal symptoms, endoscopic appearance of esophageal mucosa, and histopathological examination findings of mucosal samples showing a dense eosinophilic infiltration [7, 13, 14]. Although some controversy exists on the extent of eosinophil infiltration [15-17], recent recommendations suggest an eosinophil count ≥15 per high-power field in at least one esophageal biopsy sample and exclusion of esophageal eosinophilia secondary to GERD to be the diagnostic criteria [6, 18-21].

This study screened a large patient sample that underwent endoscopic examination and esophageal biopsy and aimed to define clinical and endoscopic characteristics of adult patients diagnosed with eosinophilic esophagitis based on recently recommended histopathological criteria.

Materials and methods

Study population

This retrospective cross-sectional descriptive study included 54 adult patients (>18 yr. of age) with a mean age of 33.6 years (range:16–61) who underwent upper gastrointestinal system endoscopy for dyspeptic complaints (epigastric pain, reflux, dysphagia, or food impaction) between January 2010 and September 2018 and diagnosed with eosinophilic esophagitis. Patients with a history of malignancy were excluded. The majority of the patients were male (81.5%). Based on previous recommendations [19], eosinophilic esophagitis was defined as an eosinophil count ≥15 per high-power field on esophageal biopsy specimens. Fifty-four patients fulfilling this criterion were included in this study and their clinical, endoscopic, and histopathological data were extracted. The study protocol was approved by the local ethics committee (Acibadem Mehmet Ali Aydinlar University Evaluation Committee for Medical Research [ATADEK], no, 2022-14/5; date, September 2, 2022) and the study was conducted in accordance with the Declaration of Helsinki.

Endoscopic biopsy assessment

All endoscopies and biopsies were done by experienced gastroenterology specialists under mild sedation. All gross examination findings, including any mucosal abnormalities, were identified and recorded, and biopsies were obtained from the esophagus, typically from multiple sites. Formalin-fixed, paraffin-embedded biopsy samples were sectioned at a thickness of 3 μm and stained with hematoxylin and eosin and PAS-AB (pH 2.5) stains. All esophageal biopsies were evaluated for reflux esophagitis, intraepithelial eosinophil infiltration, dysplasia, columnar metaplasia, and other specific conditions [22]. When intraepithelial eosinophil infiltration was seen, eosinophils were counted at the densest region using 400x high-power field. In addition, gastric biopsies were evaluated based on the histological criteria of the Sydney System [23]. Slides were also examined for the presence of *Helicobacter pylori* infection.

Statistical analysis

The results were presented with descriptive statistics. Data were expressed as mean ± standard deviation and proportions (percent, %), where appropriate.

Results

Baseline characteristics

The majority of the study population was composed of male (n = 44, 81.5%) patients. The mean age was 33.6 years (range, 16–61). The most common presenting complaint was dysphagia (61.1%), followed by dyspepsia (24.0%), regurgitation (16.6%), chest pain (16.6%), epigastric pain (12.9%), food impaction (11.1%), and halitosis (3.7%) (Table 1). The mean duration of symptoms was 6.4 (9.7) months (range, 0.5–36). History of allergy was noted in 12 (22.2%) patients, including allergic rhinitis in 7 of 12 (58.3%) patients (Table 1).

Table 1: Baseline characteristics

Age (years), mean (range)	33.6 (16-61)
Gender, n (%)	
Female	10 (18.5)
Male	44 (81.5)
Presenting symptom, n (%)	
Dysphagia	33 (61.1)
Dyspepsia	13 (24.0)
Regurgitation	9 (16.6)
Chest pain	9 (16.6)
Epigastric pain	7 (12.9)
Food Impaction	6 (11.1)
Halitosis	2 (3.7)
Duration of symptoms [a] (months), mean (SD, range)	6.4 (9.7, 0.5-36)
History of allergy, n (%)	12 (22.2)
Allergic rhinitis	7 (58.3)
Food allergy	2 (16.7)
Drug allergy	3 (25.0)

[a] Since the six patients with food impaction attended the emergency unit immediately after the incident, the mean duration of symptoms is based on data from the remaining 48 patients.

Endoscopic findings

White papules and linear furrow were the most frequent finding on endoscopic examination (35.1%) followed by circular rings (24.0%), paleness (22.2%), normal endoscopic findings (20.3%), and small caliber esophagus (11.1%) (Table 2). Two endoscopic appearance examples are shown in Figure 1.

Histopathological findings

The mean number of biopsies obtained during endoscopic examination was 4.3 (2.8) (range, 1–14). The mean eosinophil count per high-power field was 47.6 (range, 15–102). *H. pylori* data was available in 51 patients, 15 of which were

positive (29.4%) (Table 2). Examples of histopathological appearance with eosinophilic infiltration are shown in Figure 2.

Table 2: Endoscopic and histopathological findings

Distribution of endoscopic findings	n (%)
White papules	19 (35.1)
Linear furrow	19 (35.1)
Circular rings	13 (24.0)
Paleness	12 (22.2)
Normal esophagus	11 (20.3)
Food impaction	6 (11.1)
Small caliber esophagus	6 (11.1)
Number of biopsies, mean (SD, range)	4.3 (2.8, 1-14)
Eosinophil count (per high power field mean)	47.6 (15-102)
H. pylori positivity [a], n (%)	15 (29.4)

[a] For 51 cases with available data on assessment of H. pylori positivity

Figure 1: Examples of endoscopic appearance (a: food impaction, b: linear furrow).

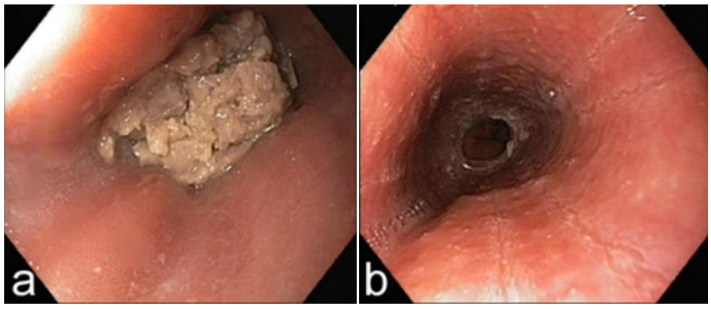
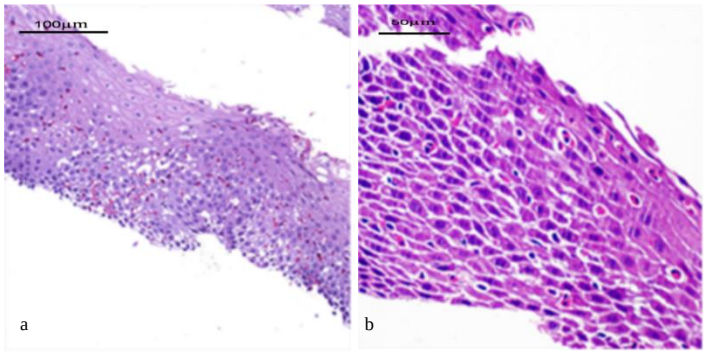


Figure 2: Histopathological appearance examples of eosinophilic infiltration (a: x40 magnification, b: x100 magnification).



Discussion

This study examined the clinical symptoms and endoscopic findings of a group of adult patients diagnosed with eosinophilic esophagitis based on the latest histopathological criteria. Our findings revealed male predominance (81.5%) in eosinophilic esophagitis and indicated dysphagia (61.1%) as the most common presenting complaint along with identification of at least two diagnostic endoscopic findings in one-third of patients.

Given that 81.5% of our cohort was composed of male patients, our findings support the male preponderance of eosinophilic esophagitis, as reported in several studies [18, 19, 24, 25], systemic reviews [26, 27], and guidelines [2, 28], although the reason remains to be specified [26].

Presenting symptoms of eosinophilic esophagitis are variable, including dysphagia, food impaction, chest pain unresponsive to anti-acids, refractory heartburn, and upper abdominal pain [2, 7, 14, 29].

Identification of dysphagia as the most prevalent complaint in our cohort is in line with several previous studies. In a US series, dysphagia was reported in 65% of patients with eosinophilic esophagitis [10]. In a Japanese study, dysphagia was the most prominent symptom reported by 46% of the patients [30]. Also, in a recent systematic review of eosinophilic esophagitis in 217 patients from Asian countries, dysphagia was reported as the primary symptom identified in 44% of the patients [26].

Nonetheless, it should be noted that most of previous studies have relatively small sample sizes along with considerable variation in the signs and symptoms reported. Being the second-most presenting complaint identified in 24.0% of our patients, dyspeptic complaints have been indicated to predominate in some patient populations [2, 29]. Also, a large Mexican study reported reflux symptoms as the most frequent presenting feature (42%) [31]. Similarly, in a Turkish study, heartburn and regurgitation was reported in 72% and 52.4% of the patients, respectively, with only 24% complaining of dysphagia [32].

Occasionally, patients may not seek help for dysphagia until food impaction occurs. The association between eosinophilic esophagitis and food impaction has been shown in previous studies, with indication of food impaction as the presenting symptom in many patients [14, 33-35].

Interestingly, in a Chinese population-based study, 1030 healthy volunteers underwent endoscopic biopsy of the esophagus, and eosinophilic esophagitis was reported in 4 (0.4%) patients [36]. Among them, only one had reflux symptoms; the remaining three patients were asymptomatic (75%). This seems to point out the fact that most eosinophilic esophagitis cases in the general population may be asymptomatic, in contrast to the findings of most previous studies, since most of clinical presentation data comes from patients who underwent endoscopic examination because of their symptoms.

Endoscopic examination with biopsy is the main diagnostic tool in eosinophilic esophagitis; however, findings are variable [2, 29]. The Eosinophilic Esophagitis Endoscopic Reference Score (EREFS; **E**dema of the mucosa, esophageal **R**ings, eosinophilic **E**xudates as white papules, linear **F**urrows, esophageal **S**tricture) has been recently validated and become an important parameter for diagnosis, clinical trials, and follow-up the patients with EoE [6, 7, 14, 20, 21, 37]. Although most patients with eosinophilic esophagitis are known to have endoscopic findings including linear furrow, circular ring, attenuation of subepithelial vascular pattern, white papules, stricture, or small caliber esophagus, many have normal esophageal appearance [35, 38]. In our study, one-third of patients had more than one endoscopic finding suggestive of the condition, emphasizing the value of gross examination of the esophagus.

Although most patients have characteristic findings, none of them were specific or pathognomonic [24, 35, 38]. Eosinophilic esophagitis may even be present in the absence of any abnormal mucosal findings [24]. In this study, approximately one-third of the patients had white papules and linear furrow; circular rings and paleness were present in 24% and 22.2% of the patients, respectively. While fibrosis in the esophageal wall with subsequent ring and stricture formation has been considered an important aspect of pathophysiology of the disease among adults [35, 38], 11.1% of our patients had a small-caliber esophagus, whereas 20% of our patients had a normal esophagus. In the study by Pasha et al., ringed esophagus was the most frequent sign (55%), followed by esophageal strictures (38%), linear furrows (33%), narrow esophagus (10%), and normal esophagus

(7%) [35]. In a Japanese study, however, longitudinal furrows were present in 35% of patients, and white papules and multiple concentric rings were found in 23% and 19%, respectively [30]. In a Turkish study, half of the patients had normal endoscopic findings, whereas the remaining cases had esophageal rings and white exudates [32].

Notably, in a systematic review of eosinophilic esophagitis in 217 patients from Asian countries, fixed concentric rings/stenosis was reported to be rare, which was likely dependent on the fact that food impaction was also a rare symptom among patients [26].

However, it should be noted that the likelihood of a normal endoscopic appearance not reflecting a truly normal esophagus has also been emphasized [36], since endoscopy has been considered to be relatively insensitive in identification of esophageal strictures, as compared with barium esophagography.

Variations in the frequency of endoscopic findings attributable to eosinophilic esophagitis in previous studies might be due to the differences in the definitions of the lesions and/or variations in the sample populations, to the stage of disease at the time of diagnosis, as well as to the relatively small sample sizes of the studies.

Allergic conditions such as allergic rhinitis, atopic dermatitis, food allergy, and asthma have been associated with esophageal esophagitis in previous studies, suggesting an allergic etiology [3-5, 39]. In the present study, twelve patients (22.2%) had a history of allergy, including food allergy, penicillin allergy, and allergic rhinitis, which supports the proposition of eosinophilic esophagitis to be categorized as an allergic disease with a genetic predisposition [2, 36, 40].

Identification *H. pylori* positivity in 29.4% of evaluated endoscopic samples in our cohort seems to align with the low rate of *H. pylori* reported among patients with eosinophilic esophagitis [26, 41, 42] and supports that eosinophilic gastrointestinal diseases have been infrequently accompanied by *H. pylori* infection [26, 43-45].

Limitations

A limitation of the present study is the small number of patients. Its retrospective design represents another limitation, where only patients with an esophageal biopsy were included, and the number of biopsies were not standardized. In addition, the retrospective design does not allow for the estimation of eosinophilic esophagitis prevalence. Future prospective studies may include all patients with esophageal complaints and a standard number of biopsies (at least four samples from mid-esophagus) may be obtained. In addition, prospective design would allow questioning allergic conditions, which may be important in early diagnosis and treatment, as well as for dietary elimination, when necessary.

Conclusions

Our findings indicate that a combination of compatible clinical, endoscopic, and histologic criteria is a mainstay in establishing the diagnosis of eosinophilic esophagitis. Given the likelihood of the prevalence of the disease to be higher than expected in the general population, along with the considerable variability in the definitions—and, thus, frequency—of endoscopic findings suggestive of the condition; the diagnosis of eosinophilic esophagitis continues to be challenging. Hence, attempts to identify a gold standard for the diagnosis seem to be one of the top priorities in the field of eosinophilic esophagitis.

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