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Original article

Eosinophilic Esophagitis among Patients with Refractory Gastroesophageal Reflux Disease

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Abstract

Background: Eosinophilic esophagitis (EoE) may be linked to gastroesophageal reflux disease (GERD) in as many as 30% of patients of EoE. The aim is to study the prevalence and clinical presentation of Eosinophilic esophagitis among patients with refractory GERD. **Methods:** This cross-sectional study was conducted on 181 patients presented with persistent GERD symptoms despite double dose PPI therapy for at least 8 weeks without interruption, who were referred to gastroenterology unit of Internal Medicine Department at Benha University Hospitals. All patients were subjected to proper and detailed history taking and thorough clinical examination, laboratory investigations including complete blood count with differential leucocytic count and upper gastrointestinal endoscopy and biopsy for histopathological examination. **Results:** The mean age of the patients was 36.7±11.46 years. One hundred and three (56.9%) patients were males and 78 (43.1%) were females. Among the studied cases, 9 (5.0%) cases had EoE and 2 (1.1%) cases had eosinophilic gastroenteritis. Peripheral eosinophilia was found in 6 (66.7%) of EoE cases. EoE cases had statistically significant higher incidence of atopy, dysphagia, food impaction, furrows, white plaques, concentric rings and strictures compared to refractory GERD patients without EoE ($P<0.05$). **Conclusions:** Our results showed that 5% of patients with refractory GERD had EoE. EoE cases had significantly higher association with history of atopy. Most patients with EoE presented with dysphagia and food impaction. Endoscopic features of EoE patients included furrows, white plaques, strictures and concentric rings. EoE cases have higher incidence of having peripheral eosinophilia at their CBCs.

Keywords: Dysphagia; Eosinophilic Esophagitis; Food Impaction; Peripheral Eosinophilia. Refractory GERD

Introduction

Eosinophilic esophagitis (EoE) is an allergic/immune response characterised by esophageal mucosal eosinophilic infiltration (≥15 eosinophils/high-power field, HPF). Its symptoms include food impaction, non-cardiac chest pain, heartburn and dysphagia. Currently, it affects 5-10 persons out of every 100,000 people per year, with a prevalence of 0.5-1 case per 1,000 people [1, 2]. White exudates or plaques, concentric rings, linear furrows as well as friability, are all endoscopic findings in EoE. Serious illness is indicated by narrowing of the lumen and strictures [3].

EoE was first characterised in children, and only lately has been seen in adults. An increasing number of people have been diagnosed with EoE throughout the years, which may be attributable to genetic and environmental changes or a greater focus on finding the condition. Patients with dysphagia and food impaction had higher rates of EoE than the general population, which may be as high as 12% in patients with dysphagia and 48% in patients with food impaction [4].

EoE may be linked to gastroesophageal reflux disease (GERD) in as many as 30% of patients of EoE. Both EoE and GERD have been identified as distinct disease entities despite their clinical similarities. Patients with GERD have eosinophilic infiltration in the esophageal mucosa, and EoE has been identified as a secondary aetiology of GERD. EoE patients benefit from topical steroids, but those with GERD benefit from gastric acid inhibitors [5].

The endoscopic reference score (EREFS) is commonly used to define the five major features of EoE (edema, rings, exudates, furrows and strictures) [6, 7]. In addition, 10 to 25 percent of individuals with EoE may have a normal endoscopic esophageal look. When there are more than 15 eosinophils per HPF, a histological diagnosis of EoE is confirmed [8].

Current guidelines propose that at least six biopsies should be taken from two separate locations, often from the distal and proximal oesophagus making the diagnostic sensitivity nearly reach 100% [9]. The "3D" idea of diet, drugs, and dilation is used in treatment [10]. For the first therapy of EoE, current United European Gastroenterology recommendations propose swallowed topical corticosteroids (STCs), high-dose proton pump inhibitor (PPI), or an elimination diet [11]. According to the Montreal Classification, refractory GERD (rGERD) is the presence of persistent troublesome GERD symptoms despite optimized double dose PPI therapy over at least eight weeks [12].

Diagnosis of GERD is usually made based on Clinical history and response to PPI therapy, but these are insufficient to make a conclusive diagnosis of GERD in isolation. According to the Lyon Consensus, diagnosis of GERD is confirmed when conclusive evidence for reflux on esophageal testing is present, including advanced grade erosive esophagitis (LA grades C and D), long-segment Barrett’s mucosa or peptic strictures on endoscopy or distal

esophageal acid exposure time (AET) >6% on ambulatory pH or pH-impedance monitoring. A normal endoscopy does not exclude GERD but provides supportive evidence refuting GERD in conjunction with distal AET <4% and <40 reflux episodes on pH-impedance monitoring off proton pump inhibitors. Reflux-symptom association on ambulatory reflux monitoring provides supportive evidence for reflux triggered symptoms and may predict a better treatment outcome when present. When endoscopy and pH or pH-impedance monitoring are inconclusive, adjunctive evidence from biopsy findings (histopathology scores, dilated intercellular spaces), motor evaluation (hypotensive lower esophageal sphincter, hiatus hernia and esophageal body hypomotility on high-resolution manometry) and novel impedance metrics (baseline impedance, post reflux swallow-induced peristaltic wave index) can add confidence for a GERD diagnosis; however, diagnosis cannot be based on these findings alone [(13)].

The definition of rGERD is controversial as it has never been clearly established. The most commonly used definition is: symptoms (retrosternal heartburn and/or regurgitation) present at least 3 times per week not responding to a double dose of PPIs for 8 weeks. It must be emphasized that this definition is only clinical, and it does not take into account the need to have objective evidence of GERD based on endoscopic findings and pH-impedance monitoring. Indeed, many patients who experience symptoms potentially related to GERD and not responding to PPI are not really affected by GERD [(14)].

We aimed to study the prevalence and clinical presentation of EoE among patients with refractory GERD.

Patients and Methods

This cross-sectional study was conducted on 181 patients aged above 18 years old [(15)], of both genders, who presented with persistent GERD symptoms as heartburn, regurgitation, dysphagia, food impaction or noncardiac chest pain despite double dose PPI therapy (pantoprazole 40 mg or equivalent bid) for at least eight weeks without interruption, those patients were referred to gastroenterology unit of Internal Medicine Department at Benha University Hospitals, Egypt. The patients provided informed written consent before participating in the study. The research was conducted within the approved guidelines of the institutional ethical committee of Benha University Hospitals (Approval code: MS 36-10-2022) during the period from December 2022 to December 2023.

The exclusion criteria were unwillingness or inability to give informed consent, corticosteroids or immunosuppressive agents consumption during the past 3 months, patients with Barrett's oesophagus, parasitic or fungal infection, carcinoma, Crohn's disease and collagen vascular diseases. All the exclusion criteria were determined depending on the history taking, clinical examination, laboratory investigations, upper gastrointestinal endoscopy and biopsies and histopathological examination of biopsy specimens.

All patients were subjected to proper and detailed history taking and thorough

clinical examination with stress on history of epigastric pain, heart burn, regurgitation, dyspepsia, dysphagia and atypical manifestations of GERD as non-cardiac chest pain, reflux cough and reflux asthma, duration of symptoms, type and duration of GERD treatment, adherence to the treatment and history of atopy. Laboratory investigations included complete blood count (CBC) with differential leucocytic count, eosinophilia was considered when absolute eosinophil count exceeded 500/µL in peripheral blood [16]. Serum creatinine, ALT, AST, CRP, ESR and stool analysis were also performed.

Upper gastrointestinal endoscopy and biopsy for histopathological examination:

Patients stopped PPI therapy for 2 weeks prior to endoscopy. Fasting 12 hours before the endoscopy. Sedation with administration of 2mg midazolam with increments of 1mg given slowly intravenous at rate of approximately 1mg/30 seconds. Dose can be increased up to 5mg. Six biopsies were taken from lower and mid esophagus (three from each) and from every visible lesion, also biopsies were taken from gastric antrum to mostly exclude eosinophilic gastroenteritis and increase the diagnostic specificity, as suggested in the 2007 consensus [17]. Samples were collected separately into formalin regarding to the site of biopsy, and then transferred to the pathology department of Benha University Hospitals, where samples underwent hematoxylin and eosin staining and pathological examination. Cases with more than 15 eosinophils per HPF or eosinophilic microabscess (aggregation of 3–4 eosinophils) was diagnosed as eosinophilic esophagitis and cases with more than 20 eosinophils per HPF at gastric biopsies associated with presence of more than 15 eosinophils per HPF at their esophageal biopsies were considered eosinophilic gastroenteritis [18].

Sample size:

The sample size was calculated using Epi-Info (Epidemiological information package) software version 7.2.5.0. Based on a previous study done by ***García-Compeán et al.*** [19], which investigated the prevalence of eosinophilic esophagitis in patients with refractory gastroesophageal reflux disease symptoms and reported that six out of 150 included patients (4%) met the diagnostic criteria for EoE. So, with expected frequency 4% and acceptable margin of error of 3% and level of confidence of 95%, the total sample size will be 164 patients. Allowing for drop out or missed data of about 10%, the sample size was adjusted and increased to 181 patients.

Statistical analysis:

The collected data was revised, coded, and tabulated using SPSS, Version 25.0 (Armonk, NY: IBM Corp.). Data were presented and suitable analysis was done according to the type of data obtained for each parameter. Mean, standard deviation (± SD), median, and range were used for numerical data. Frequency and percentage were used for non-numerical data. Student T test was used to assess the statistical significance of the difference between two study group

means [20]. Mann Whitney test (U test) was used to assess the statistical significance of the difference of a non-parametric variable between two study groups [21]. Chi-Square test was used to examine the relationship between two qualitative variables. Fisher Exact or Monte Carlo tests were used to examine the relationship between two qualitative variables when the expected count is less than 5 in more than 20% of cells [22]. A p value is considered significant if <0.05 at confidence interval 95%.

Results

Regarding age, the mean age of the refractory GERD cases was 36.7 ± 11.46 years and ranged from 19 to 56 years. Regarding sex, 103 (56.9%) were males, and 78 (43.1%) were females. **Table 1**

The mean duration of symptoms in these cases was 9.30 ± 6.32 years, with a range from 1 to 25 years. The mean duration of continuous PPI therapy was 9.11 months ± 4.65 months, with a range from 3 to 24 months. Among the studied cases, 16 (8.8%) patients had peripheral eosinophilia. **Table 2**

Among the studied cases, 9 (5.0%) cases had EoE. **Figure 1**

Only 1.1% (2 cases) among the refractory GERD cases had eosinophilic gastroenteritis. **Figure 2**

There was no statistically significant difference in age and sex between EoE cases and those who did not have EoE. **Table 3**

EoE cases had significantly higher association with history of atopy (P<0.05). Dysphagia and food impaction were significantly more common in EoE patients (P<0.05). For symptoms like heartburn, regurgitation, dyspepsia, non-cardiac chest pain, ENT symptoms, and respiratory symptoms, there were no statistically significant differences between the EoE and non-EoE groups, as evidenced by non-significant p values (p>0.05). The percentages of patients reporting these symptoms were roughly equal between the two groups. Furrows, white plaques, strictures and concentric rings were significantly more commonly present in refractory GERD cases with EoE compared to those without EoE (P<0.05). On the other hand, the presence of esophagitis, hiatus hernia and ulcer did not appear to be significantly associated with EoE in refractory GERD cases. **Table 4**

There was no significant difference in the duration of symptoms between the two groups of patients. Refractory GERD cases with EoE had higher incidence of having peripheral eosinophilia at their CBCs compared to those without EoE (P<0.001). **Table 5**

Table 1: Demographic data of studied refractory GERD cases

		Refractory GERD (N=181)
Age (years)		36.7±11.46
Sex	**Male**	103 (56.9%)
	Female	78 (43.1%)

Data presented as mean ± SD or frequency (%)

Table 2: Duration of symptoms and continuous PPI therapy, peripheral eosinophilia, eosinophilic gastroenteritis prevalence and EoE prevalence among studied refractory GERD cases

	Refractory GERD (N=181)	
Duration of symptoms (years)	9.30 ± 6.32	
	8 (1-25)	
Duration of continuous PPI therapy (months)	9.11±4.65	
	8(3-24)	
Peripheral eosinophilia	16	8.8%

Data presented as mean ± SD, median (range) or frequency (%)

Table 3: Comparison of demographic data between those with and without EoE

		Refractory GERD		P value
		No EoE (N=172)	**EoE (N=9)**	
Age (years)		37.19 ±11.38	33.78 ± 9.69	0.379
Sex	**Male**	98 (57.0%)	5 (55.6%)	0.933
	Female	74 (43.0%)	4 (44.4%)	

Data presented as mean ± SD, median (range) or frequency (%)

Table 4: Comparison of history of atopy, clinical manifestations and endoscopic findings of esophagus between those with and without EoE

		Refractory GERD				P value
		No EoE (N=172)		**EoE (N=9)**		
Atopy history	**History of atopy**	19	11.0%	6	66.7%	<0.001*
	Bronchial asthma	5	2.9%	2	22.2%	0.041*
	Urticaria	5	2.9%	2	22.2%	0.041*
	Atopic dermatitis	3	1.7%	0	0.0%	0.690
	Food allergy	3	1.7%	3	33.3%	0.002*
	Rhinoconjunctivitis	5	2.9%	4	44.4%	<0.001*
Clinical manifestations	**Heart burn**	124	72.1%	6	66.7%	0.713
	Dysphagia	47	27.3%	7	77.8%	0.003*
	Regurgitation	92	53.5%	5	55.6%	0.904
	Food impaction	40	23.3%	5	55.6%	0.044*
	Dyspepsia	104	60.5%	4	44.4%	0.488
	Non cardiac chest pain	63	36.6%	4	44.4%	0.728
	ENT symptoms	33	19.2%	3	33.3%	0.385
	Respiratory symptoms	26	15.1%	2	22.2%	0.631
Endoscopic findings of esophagus	**Furrows**	37	21.5%	6	66.7%	0.006*
	White plaques	32	18.6%	6	66.7%	0.003*
	Stricture	4	2.3%	4	44.4%	<0.001*
	Concentric Rings	22	12.8%	5	55.6%	0.004*
	Esophagitis	81	47.1%	5	55.6%	0.738
	Hiatus hernia	78	45.3%	1	11.1%	0.080
	Ulcer	16	9.3%	1	11.1%	0.597

Data presented as frequency (%), *: statistically significant as P value <0.05

Table 5: Comparison of duration of symptoms and the presence of peripheral eosinophilia between those with and without EoE

	Refractory GERD		P value
	No EoE (N=172)	**EoE (N=9)**	
Duration of symptoms (years)	9.42 ± 6.22	8.34 ± 4.16	0.608
	8 (1-25)	7 (2-20)	
Peripheral eosinophilia	10 (5.8%)	6 (66.7%)	<0.001*

Data presented as mean ± SD, median (range) or frequency (%)

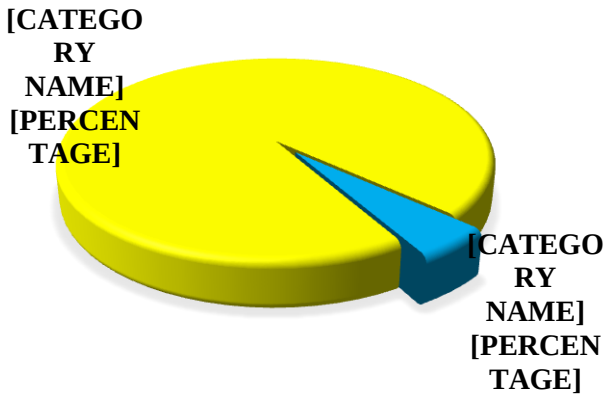

Figure 1: EoE prevalence among studied refractory GERD cases.

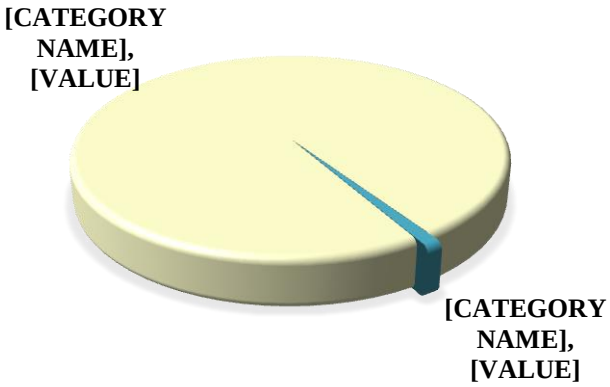

Figure 2: Eosinophilic gastroenteritis prevalence among studied refractory GERD cases.

Discussion

Refractory GERD is presence of GERD symptoms (retrosternal heartburn and/or regurgitation) at least 3 times per week not responding to a double dose of PPIs for 8 weeks [23]. EoE is one of the main causes of refractory GERD that presents with symptoms of esophageal dysfunction and is a major cause of food impaction, heartburn and dysphagia [1, 2].

In the present study, the percentages of refractory GERD cases with heart burn, dysphagia, regurgitation, food impaction, dyspepsia, non-cardiac chest pain, ENT symptoms and respiratory symptoms were 71.8%, 29.8%, 53.6%, 24.9%, 59.7%, 37%, 19.9% and 15.5% respectively.

Our results were in agreement with others [24], who observed that the main symptoms experienced by patients were heartburn (80.8%), regurgitation (65.8%), and atypical symptoms (53.4%). However, ***Anis et al.*** [25] reported that dysphagia was the chief complaint leading to EGD followed by food impaction and heartburn.

In the current study, the mean duration of symptoms in these cases was 9.30 ± 6.32 years. The mean duration of continuous PPI therapy was 9.11 ± 4.65 months.

While in the study by ***Anis et al.*** [25], the median duration of symptoms was 46.5 months (range: 22-65 months).

In the present study, among the refractory GERD cases, 9 cases (5.0%) had EoE. On the other hand, 172 cases (95.0%) did not have EoE.

Our results were in agreement with ***García-Compeán et al.*** [19], who reported that 4% cases of refractory GERD were diagnosed with EoE on endoscopy. ***Hunter et al.*** [26], reported that the prevalence of EoE among patients presenting with upper gastrointestinal symptoms was 3.3% (3 cases) with an overlap between erosive reflux disease and EoE in one patient. However, ***Sá et al.*** [27] reported that only 1/103 patients (0.97%) with PPI-refractory GERD was diagnosed with EoE. The patient was positive for atopy and endoscopy revealed esophageal mucosa corrugations.

In the study by ***Anis et al.*** [25], there were 209 esophageal biopsies performed in patients with refractory GERD. Of these patients, 16 (7.7%) were diagnosed with EoE. Similarly, ***Saeed et al.*** [28] reported that the incidence of EoE among patients undergoing upper gastrointestinal endoscopy for any reason was reported to be 7.4%. ***Foroutan et al.*** [29] reported that the prevalence of EoE in cases of refractory GERD was 8.8%.

In the current study, there was an insignificant difference between refractory GERD cases without EoE and those with EoE regarding age and sex.

Our results were in agreement with ***Okimoto et al.*** [30] who reported that there were no significant differences between EoE group and non-EoE group as regards to age and sex. However, ***García-Compeán et al.*** [19] compared the characteristics of patients with and without EoE and found that patients with EoE were significantly younger. In 2019 researchers [25], found that eosinophilic esophagitis was more common in women than men (5: 3) with an age range of 41-63 years. These results suggest that the role of gender in eosinophilic esophagitis is still unclear.

In the current study, EoE cases had significantly higher association with history of atopy. Our results were matched with previous studies [31] which reported that allergic rhinitis, and atopic dermatitis were more common in EoE positive patients. While others [30] reported that there were no significant differences between EoE group and non-EoE group as regards to history of allergy.

In the present study, dysphagia and food impaction were significantly more common in EoE patients, compared to the non-EoE group. For symptoms like heartburn, regurgitation, dyspepsia, non-cardiac chest pain, ENT symptoms, and respiratory symptoms, there were no statistically significant differences between the EoE and non-EoE groups.

In the same way, a study [28] reported that patients with EoE had significantly more dysphagia and food impaction.

In the current study, furrows, white plaques, strictures and concentric rings were more commonly present in refractory GERD cases with EoE compared to those without EoE. On the other hand, the presence of esophagitis, hiatus hernia and esophageal ulcer did not appear to be significantly associated with EoE in refractory GERD cases.

There was no significant difference in the duration of symptoms between the two groups of patients.

In the same way, it was reported that patients with EoE had significantly more esophageal rings and esophageal strictures than patients without EoE [(19)]. It was reported that the common endoscopic findings in EoE were erosive esophagitis, rings, and white plaques [(29)].

Our findings revealed that there was a significant difference between cases without EoE, and those with EoE regarding peripheral eosinophilia, suggesting that refractory GERD cases showing peripheral eosinophilia at their CBCs have higher probability of having EoE.

Our results were in agreement with the study done in 2006 [(32)], which reported a significant correlation between an increase of eosinophils in the blood and esophageal tissue. However, this examination can only be used as a predictor of the severity of esophagitis symptoms. It was proven that the number of eosinophils in the blood decreased after therapy, accompanied by improvement in symptoms. While in a more recent study done in 2022[(33)] it was reported that no correlation between peripheral blood eosinophil level and esophageal tissue was found ($p>0.466$).

Limitations

Our study had some limitations as single center study with relatively small sample size.

Conclusions

Our results showed that 5% of patients with refractory GERD had EoE. EoE cases had significantly higher association with history of atopy, and most of them presented with dysphagia and food impaction.

Recommendation

We recommend that patients with GERD not responding to optimized double dose PPI therapy for at least 8 weeks, having history of atopy, showing peripheral eosinophilia at their CBCs, presenting with dysphagia or food impaction must be considered for EoE screening via EGD and esophageal biopsies.

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