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Prevalence of esophageal eosinophilia in patients referred for diagnostic upper gastrointestinal endoscopy

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Abstract

Background: Several conditions are associated with esophageal eosinophilia such as eosinophilic esophagitis (EoE) and gastro-esophageal reflux disease (GERD). The aim of this study was to detect the prevalence of esophageal eosinophilia in patients with upper gastrointestinal (GI) symptoms referred for diagnostic upper GI endoscopy. This study included 86 patients who underwent upper GI endoscopy and biopsies.

Results: Esophageal eosinophilia EE was found in 26 patients (30.2%): 3 patients (3.5%) had EoE and 23 patients (26.7%) had low-grade esophageal eosinophilia. The most common presenting symptoms were heart burn in 84 patients (97.7%) and upper abdominal pain in 78 patients (90.7%). Reflux esophagitis (ERD) was observed in 18.6% of patients. In histopathological examination, EoE was found in 3.5%, mild reflux esophagitis in 37.2%, and severe reflux esophagitis in 16.3%. There is statistically significant correlation between EE and male sex, hypertension, dysphagia, hiatus hernia, incompetent cardia, and fixed rings. Age, incompetent cardia, and dysphagia were statistically significant independent predictors of low-grade EE.

Conclusion: Esophageal eosinophilia EE was found in 30.2% of patients: 3.5% had eosinophilic esophagitis EoE and 26.7% had low-grade esophageal eosinophilia.

Keywords: EE, EoE, GERD

Background

Under physiological conditions, eosinophils are present throughout the gastrointestinal tract distal to the squamous esophagus [1]. Several conditions are associated with esophageal eosinophilia (EE) such as eosinophilic esophagitis (EoE), gastro-esophageal reflux disease (GERD), eosinophilic gastritis, gastroenteritis, or colitis with esophageal involvement, esophageal motility disorders such as achalasia, Crohn's disease with esophageal involvement, infections (fungal, viral), and hypereosinophilic syndrome [2, 3]. In the clinical setting, some of

them are frequent such as GERD and EoE [2]. Eosinophilic esophagitis was first reported as the esophageal involvement of eosinophilic gastroenteritis (EGE) in 1977. Thereafter, this condition had been considered a subtype of (GERD). In 1993, Attwood et al. published the first case series of EoE as a distinct disease entity different to GERD or secondary EE [4]. Several risk factors and mechanisms have been described by which external environmental agents and factors inherent to each person may lead to EoE. The diagnosis of EoE requires all of the following: symptoms related to esophageal dysfunction, eosinophil-predominant inflammation on esophageal biopsy, characteristically consisting of a peak value of ≥ 15 eosinophils per high-power field (HPF) (or 60 eosinophils per mm^2), and exclusion of other causes that may be responsible for or contributing to symptoms and

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esophageal eosinophilia [2]. The most common symptom of EoE in adults is dysphagia [5]. Endoscopic findings of EoE are frequently described using the EoE endoscopic reference score (EREFS), which stands for the five key findings (edema, rings, exudates, furrows, and strictures) [6]. In addition, the endoscopic appearance of the esophagus may be normal in 10 to 25% of patients with EoE [7]. A histological diagnosis is confirmed when there are ≥ 15 eosinophils per high-power field (HPF) [2]. Currently, the recommendation is to take at least six biopsies from two different sites, typically from the distal and proximal esophagus [8]. The diagnostic sensitivity increased to almost 100% with five or more biopsies [4]. The therapeutic approach consists of the “3D” concept: diet, drugs, and dilation [4]. Current United European Gastroenterology guidelines recommend swallowed topical corticosteroids (STCs), high-dose PPI, or elimination diet for the initial treatment of EoE [9]. GERD has been defined by the Montreal Classification as a condition that occurs due to retrograde flow of gastric contents into the esophagus that lead to troublesome symptoms, which are typically heartburn and regurgitation [10]. GERD can be classified as erosive reflux disease (ERD) or non-erosive reflux disease (NERD) [11].

Objectives

To detect the prevalence of esophageal eosinophilia in patients with upper GI symptoms referred for diagnostic upper GI endoscopy.

Methods

Study design

The present study was a cross-sectional prevalence study.

Settings

The study was conducted at Mansoura Specialized Medical Hospital.

Participants

This study included 86 adult patients with unexplained upper GI symptoms referred for diagnostic upper GI endoscopy at Mansoura Specialized Medical Hospital.

Variables

Inclusion criteria

Adult patients (> 18 years) with unexplained upper GI symptoms (dysphagia, heartburn, nausea, vomiting, and upper abdominal pain) referred for diagnostic upper GI endoscopy at Specialized Medical Hospital, Mansoura University.

Exclusion criteria

Patients with the following:

- Advanced heart failure.
- Chronic liver disease.
- Chronic kidney disease.

Malignancy.

- Other causes of esophageal eosinophilia as achalasia, Crohn’s disease and infections such as candidal esophagitis, connective tissue disorders, and hypereosinophilic syndrome.

Data sources/measurement

All selected patients were subjected to careful history taking, physical examination, laboratory tests including complete blood count (CBC), differential leucocytic count, serum creatinine, liver biochemical tests, abdominal ultrasound, upper GI endoscopy (esophagitis endoscopic reference score was used to minimize observer variability), biopsy (6 esophageal and 4 antral biopsies) and lastly, histopathological examination by staining the biopsies with hematoxylin and eosin (H&E). On the high-power field, the pathologist counted the eosinophils. The presence of more than 15 eosinophils/HPF was diagnostic for EoE and presence of less than 15 eosinophils/HPF indicates low-grade EE.

Bias

N/A

Study size

The study size is determined by the statistician.

Quantitative variables

N/A

Statistical methods

Data were entered and analyzed using IBM-SPSS software (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.)

Results

EE was found in 26 patients (30.2%): 3 patients (3.5%) had EoE and 23 patients (26.7%) had low-grade esophageal eosinophilia as shown in Table 1.

The most common presenting symptoms were heart burn in 84 patients (97.7%) and upper abdominal pain in 78 patients (90.7%) as shown in Table 1.

Reflux esophagitis (ERD) was observed in 18.6% of patients as shown in Table 1.

Table 1 Descriptive statistics of demographic, clinical, endoscopic and histopathological parameters of the studied cases (N = 86)

Variable	N	%
Residence:		
rural	62	72.1
urban	24	27.9
Heart burn	84	97.7
Upper abdominal pain	78	90.7
Nausea	42	48.8
Vomiting	24	27.9
Dysphagia	22	25.6
Unintentional weight loss	5	5.8
Current smoking	14	16.3
Atopy	8	9.3
DM	4	4.7
Hypertension	10	11.6
NSAIDs use	8	9.3
PPI use	76	88.4
PPI duration (months) median (min.-max.)	3	(0-12)
Reflux oesophagitis	16	18.6
Grade A	10	11.6
Grade B	4	4.7
Grade C	2	2.3
Incompetent cardia	42	48.8
Hiatus hernia	8	9.3
Fixed rings (Trachealization)	6	7
Gastritis	59	68.6
Antral gastritis	45	52.3
Pan gastritis	14	16.3
Histopathologically Oesophagitis	46	53.5
Mild	32	37.2
Severe	14	16.3
Eosinophilic oesophagitis (eosinophils ≥ 15/HPF)	3	3.5
Basal cell hyperplasia		
< 15%	48	55.8
15-30%	34	39.5
> 30%	4	4.7
Papillary elongation		
< 50%	70	81.4
50-75%	16	18.6
Dilated intercellular space		
Absent	36	41.9
< one lymphocyte diameter	40	46.5
≥ one lymphocyte diameter	10	11.6
Intraepithelial eosinophils		

Table 1 Descriptive statistics of demographic, clinical, endoscopic and histopathological parameters of the studied cases (N = 86) (Continued)

Absent	60	69.8
1-2 cells	20	23.3
> 2 cells	6	7
Intraepithelial neutrophils		
Absent	82	95.3
1-2 cells	2	2.3
> 2 cells	2	2.3
Intraepithelial mononuclear cells		
0-9 cells	86	100
Chronic gastritis	70	81.4
H. pylori-associated gastritis	42	48.8
Descriptive statistics of clinico-demographic, laboratory, endoscopic and histopathological parameters the three eosinophilic oesophagitis cases (EoE) (N = 3)		
Characteristic	Statistic	
Sex	All were male patients	
Age range	34-73 years	
Current smoking	1 (33.3%)	
DM, hypertension and atopy	None	
NSAIDs use	None	
PPI use (Duration range in months)	All (2-4 months)	
Dysphagia	All	
Upper abdominal pain and heart burn	All	
Nausea and vomiting	None	
Unintentional weight loss	None	
WBC count range	5.8-6.3	
Eosinophil count range	0.05-0.1	
Eosinophilia	Mild eosinophilia in 1 case	
Hemoglobin level range	13.3-14.0	
Platelet count range	172-285	
Hiatus hernia and incompetent cardia	1 (33.3%)	
Fixed rings	2 (66.7%)	
Reflux oesophagitis (ERD)	None	
Basal cell hyperplasia	Present (15-30% of total thickness)	
Papillary elongation	Normal (< 50%) in all	
Dilated intercellular space	Dilated (< 1 lymphocyte) in all	
Intra epithelial eosinophils	≥15/HPF in all	
Intra epithelial neutrophils	> 2 cells in 1 patient No cells in the two other patients	
Intra epithelial mononuclear cells	Not present	

Table 1 Descriptive statistics of demographic, clinical, endoscopic and histopathological parameters of the studied cases (N = 86) (Continued)

reflux oesophagitis (histologically)	Severe reflux esophagitis in 1 patient. No reflux in 2 other patients
H. pylori-associated chronic gastritis	All

In histopathological examination, EoE was found in 3.5%, mild reflux esophagitis in 37.2%, and severe reflux esophagitis in 16.3% as shown in Tables 1 and 1.

There is statistically significant correlation between EE and proportions of male sex, hypertension, dysphagia, hiatus hernia, incompetent cardia, and fixed rings as shown in Table 2.

Age, incompetent cardia, and dysphagia were statistically significant independent predictors of low-grade EE as shown in Table 3.

This table showed that 62 patients (72.1%) live in rural areas and 24 patients (27.9%) in urban areas. The most common symptoms were heart burn in 84 patients (97.7%) and upper abdominal pain in 78 patients (90.7%), while dysphagia was observed in 22 patients (25.6%). Current smoking in 14 (16.3%) patients, atopy in 8 (9.3%), and PPI use in 76 (88.4%) patients with median duration of 3 months (0–12).

On endoscopic examination, reflux esophagitis was observed in 18.6%, incompetent cardia in 48.8% and fixed rings in 7% of patients. Gastritis was observed in 59 patients 68.6% (45 antral and 14 pan gastritis).

On histopathological examination, EE was found in 26 patients (30.2%): 3 patients (3.5%) had EoE and 23 patients (26.7%) had low-grade esophageal eosinophilia (< 15 eosinophils/HPF). Mild reflux esophagitis was found in 37.2%, severe reflux esophagitis in 16.3%, and H. pylori-associated gastritis in 48.8% of cases.

This table shows that EoE cases were males, and their age range from 34 to 73 years. One patient was a smoker. All 3 patients had recent history of PPI use (for 2–4 months). All patients had dysphagia, upper abdominal pain, and heart burn. No one had atopy. No one had peripheral eosinophilia. WBCs, hemoglobin, and platelets were within normal range. In upper GI endoscopy, 2 patients had fixed rings while 1 patient had normal appearing mucosa. Incompetent cardia and hiatus hernia were observed in 1 patient. ERD was not observed in any patient. According to histopathological findings, basal cell hyperplasia and dilated intercellular space were observed in all patients, but there was no papillary elongation. Intra epithelial eosinophils were ≥ 15 .

Table 2 Correlation between EE as an ordinal variable and dichotomous study variables

Study variable	Correlation coefficient	P value
Rank biserial correlation (dichotomous variables)	r_{rb}	
Marital status	0.025	0.817
Sex	– 0.246	0.022
Residence	0.185	0.088
Diabetes mellitus	0.086	0.431
Hypertension	0.217	0.045
Atopy	0.125	0.252
NSAIDs use	0.125	0.252
PPI use	– 0.066	0.548
Dysphagia	0.336	0.002
Nausea	– 0.056	0.607
Vomiting	0.026	0.812
Heartburn	0.101	0.355
Abdominal pain	0.042	0.699
Chronic gastritis	– 0.186	0.086
H. pylori	– 0.011	0.923
Hiatus hernia	0.485	< 0.001
Incompetent cardia	– 0.348	0.001
Fixed rings	0.452	< 0.001
Weight loss	– 0.084	0.429

Table 3 Predictors of the likelihood of low-grade EE vs absent EE

Predictor	Univariate			Multivariate		
	P value	COR	95% CI	P value	OR	95% CI
Age (years)	0.002			0.019		
< 46 years		R	R		R	R
≥ 46 years		5.2	1.8–14.7		4.4	1.3–15
Cardia	0.001			0.007		
Competent		R	R		R	R
Incompetent		8.2	2.5–27.2		5.8	1.6–20.9
Dysphagia	0.034			0.033		
Absent		R	R		R	R
Present		3.2	1.1–9.4		4.3	1.1–16.6
Hypertension	0.023			0.203		
Absent		R	R		R	R
Present		4.9	1.2–19.6		2.7	0.583–12.6

R = reference category, COR = crude odds ratio, OR = odds ratio, CI = confidence interval, P value binary logistic regression

There was severe reflux esophagitis in the patient. All 3 patients had *H. pylori* in gastric biopsy.

This table showed a statistically significant correlation between EE and proportions of male sex, hypertension, dysphagia, hiatus hernia, incompetent cardia, and fixed rings.

As the proportions of male sex, hypertension, dysphagia, hiatus hernia, incompetent cardia, and fixed rings go up, the grading of EE goes up. No statistically significant correlation with other dichotomous variables.

This table showed the results of binary logistic regression analysis that was run to ascertain the effects of age ≥ 46 years, incompetent cardia, presence of dysphagia, and hypertension on the likelihood that participants will exhibit low-grade EE. Univariate analysis showed that each of the four predictor variables was statistically significant. On running multivariate analysis, only age, incompetent cardia, and dysphagia were statistically significant independent predictors of low-grade EE.

The model was statistically significant ($\chi^2 [4] = 27.338$, $P < 0.001$).

The model correctly classified 75.9% of cases with sensitivity of 56.5% and specificity of 83.3%.

Participants with older age (≥ 46), incompetent cardia, and dysphagia had 4.4, 5.8, and 4.3 times higher odds to exhibit low-grade EE.

Participants

This study included 86 adult patients with unexplained upper GI symptoms referred for diagnostic upper GI endoscopy at Mansoura Specialized Medical Hospital.

Descriptive data, outcome data, and main results

Descriptive data, outcome data, and main results are shown in Tables 1, 2 and 3.

Other analyses

N/A

Key results

EE was found in 26 patients (30.2%): 3 patients (3.5%) had EoE and 23 patients (26.7%) had low-grade esophageal eosinophilia.

The most common presenting symptoms were heart burn in 84 patients (97.7%) and upper abdominal pain in 78 patients (90.7%). Reflux esophagitis (ERD) was observed in 16 patients (18.6%). In histopathological examination, EoE was found in 3 patients (3.5%), mild reflux esophagitis in 32 patients (37.2%), and severe reflux esophagitis in 14 patients (16.3%). EoE patients were 3 males and had dysphagia but no history of atopy. Two EoE patients had fixed rings while 1 patient had normal appearing mucosa. There is statistically significant correlation between EE and proportions of male sex,

hypertension, dysphagia, hiatus hernia, incompetent cardia, and fixed rings. Age, incompetent cardia, and dysphagia were statistically significant independent predictors of low-grade EE.

Discussion

The present study included 86 patients with upper GI symptoms referred for upper GI endoscopy. Eosinophils are not present in the esophagus under normal conditions [1]. Eosinophilic esophagitis diagnosis should be confirmed histologically based on the presence of more than 15 eosinophils per high-power field and the exclusion of other causes of eosinophilia [7].

Therefore, the aim of our study was to detect the prevalence of esophageal eosinophilia in patients with upper gastrointestinal (GIT) symptoms referred for diagnostic upper GIT endoscopy. In the current study, 14 patients (16.3%) were smokers, 4 patients (4.7%) had D.M, 10 patients (11.6%) had hypertension, 8 patients (9.3%) had atopy, 8 patients (9.3%) had history of recent NSAIDs use, and 76 patients (88.4%) were with recent history of PPIs use with median duration of 3 months. In similar study conducted by Hunter et al. (2014) [12] on 91 adult patients presenting with various upper gastrointestinal symptoms, they found that 61.5% of patients were males and 38.4% were females. One third of the patients gave history of smoking and 71% gave history of PPIs use. In our study, the most common presenting symptom was heart burn which is present in 84 patients (97.7%) followed by upper abdominal pain in 78 patients (90.7%). In contrast, in an Egyptian study conducted in El-Minia University, the upper abdominal pain was the most common symptom and reported in 63.3% then heartburn in 50% of patients [13]. In our study, the most common histopathological finding was that of reflux esophagitis which was found in 46 cases (53.5%): mild reflux esophagitis in 32 cases (37.2%) and severe reflux esophagitis in 14 cases (16.3%). EoE was observed in 3 cases (3.5%); 1 case of them has histopathological findings of reflux esophagitis. Thirty-eight cases had normal esophageal biopsy. *H. pylori* was found in 42 cases (48.8%) of cases.

In our study, we found 26 cases (30.2%) with EE, 3 cases (3.5%) had high-grade esophageal eosinophilia (≥ 15 /HPF) which fulfill the diagnostic criteria of eosinophilic esophagitis, 23 cases (26.7%) had low-grade esophageal eosinophilia (< 15 /HPF), but 60 cases (69.8%) had absent esophageal eosinophilia.

Also, there is an Egyptian study that showed the prevalence of EoE in patients with upper GI symptoms was 1.8% [13].

This discrepancy in prevalence rate is related to many factors: first, differences in demographic data

(i.e., age group, gender predominance, race, and ethnicity) of patients included in each study; second, using different diagnostic criteria of eosinophilic esophagitis; and third, the complex interplay between eosinophilic esophagitis and GERD which can lead to many conflicting results [14].

In our study, the 3 cases of eosinophilic esophagitis were male, and their age range was from 34 to 73 years. One case was a smoker. All 3 cases had recent history of PPI use (for 2–4 months).

All 3 patients had dysphagia, upper abdominal pain, and heart burn. None had atopy nor peripheral eosinophilia.

Sawada et al. (2019) [15] analyzed a total of 106 patients with EoE and a median age of 46 years (range 41–52). Similarly, the majority of patients were male (65%) and most patients (89%) had symptoms including dysphagia (69%). However, heartburn and chest pain represented (25 and 15%), respectively, and 70% of patients had comorbidities of allergic diseases.

In agreement with our study, Fouad et al. (2018) [13] had found that EoE is more common in males than in females (3:1) with mean age 34.3 ± 6.0 years. But no one was smoker and all had normal stomach and duodenal endoscopic findings.

In the present study, reflux esophagitis (ERD) was observed in 18% by endoscopy while by biopsy, we found mild reflux esophagitis in 37.2% and severe reflux esophagitis in 16.3% in spite of normal appearing mucosa.

So, it is suggested to obtain an endoscopic biopsy in spite of normal appearing lower esophageal mucosa in patients with GERD symptoms, in those with incompetent cardia, in those who are currently smoking, or in those with hiatus hernia, particularly in male patients.

In our study, we found statistically significant correlation between EE and proportions of male sex, hypertension, dysphagia, hiatus hernia, incompetent cardia, and fixed rings.

Also age, incompetent cardia, and dysphagia were statistically significant independent predictors of low-grade EE.

Similarly, Ravi et al. 2011 [16] found that patients with low-grade esophageal eosinophilia were older (48 ± 2.1) and showed a male predominance. Dysphagia was the most common presenting symptom as present in 83% of patients, and the fixed esophageal rings was the most common endoscopic finding, as seen in 37% of patients.

In the current study, the fixed rings (trachealization) were present in 6 patients (7%): 2 of them were diagnosed to have EoE and the other 4 patients had low-grade EE. This can be explained by that the fixed rings are non-pathognomonic as mentioned by Braunberger et al. (2020) [17]. Our 3 EoE cases had recent history of PPI use (for 2–

4 months) with no improvement of their symptoms which exclude PPI-responsive esophageal eosinophilia (PPI-REE) as there are no significant clinical, histological, and endoscopic characteristics that distinguish PPI-REE from EoE (Eluri and Dellon 2015) [18] despite the efficacy of PPI as stated by Young, 2020 [19].

Limitations

Considering the limited subjects, only 86 patients were included in the study, so our results should be interpreted with caution. Further studies are needed to evaluate patients with low-grade eosinophilia.

Interpretation

Our results should be interpreted with caution because of several limitations. We recruited 86 patients in this study, and the sample size is relatively small which may restrict the subgroups analysis. All participants were from Mansoura Specialized Medical Hospital which may not stand for all the Egyptian population.

Generalizability

The fundamental experiments should be further conducted to validate our results and explore the possible mechanism.

Conclusion

EE was found in 26 patients (30.2%): 3 patients (3.5%) had EoE and 23 patients (26.7%) had low-grade EE. EoE prevalence has evolved in the last 2 decades and varies according to different population. Many predictors for low-grade EE has been identified but still its clinical significance is not clearly defined and further studies are recommended.

Abbreviations

EE: Esophageal eosinophilia; EoE: Eosinophilic esophagitis; GERD: Gastro-esophageal reflux disease; ERD: Erosive reflux disease; NERD: Non-erosive reflux disease; GI: Gastrointestinal; HPF: High-power field; H&E: Hematoxylin and eosin; DM: Diabetes mellitus; PPI: Proton pump inhibitor; PPI-REE: PPI-responsive esophageal eosinophilia; EGE: Eosinophilic gastroenteritis

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Authors' contributions

NAFA: manuscript review, editing, design, and publishing. HAMA: literature search, clinical follow-up, and statistics. DAAI: histopathological studies. IAEE: idea of the study and data collection. All authors have read and approved the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study protocol was investigated and approved by the Medical Ethics Research Team, Faculty of Medicine, Mansoura University (code number: MS.18. 12.392). Every case, after guaranteeing privacy, has been given verbal consent as most of the patients cannot read or write.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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