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 mm²), and exclusion of other causes that may be responsible for or contributing to symptoms and...
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 heartburn 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

| Characteristic                  | Statistic          |
|---------------------------------|--------------------|
| Sex                             | All were male      |
| 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    | 215/HPF in all     |
| Intra epithelial neutrophils    | > 2 cells in 1 patient |
| Intra epithelial mononuclear cells | Not present       |
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 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                                                               |

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

| Study variable                  | Correlation coefficient | P value |
|---------------------------------|-------------------------|---------|
| 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 \( \geq 46 \) 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 \( (\geq 46) \), 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 heartburn 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 heartburn 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 \( (\geq 15/HPF) \), 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...
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; Gl: 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: contributions

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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