ORIGINAL ARTICLE

Prevalence of Eosinophilic Esophagitis in Adult Patients with Esophageal Symptoms at a Tertiary Centre in Northwest India

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ABSTRACT

Background and Aims: Eosinophilic esophagitis (EoE) is a chronic inflammatory disease. This study was aimed to evaluate the prevalence of EoE in adults at a tertiary care centre in north-west part of India.

Methods: Patients with esophageal symptoms including retrosternal discomfort, heartburn, dysphagia to solids and history of food bolus impaction for at least 4 weeks were prospectively screened. We excluded patients of infectious esophagitis, recent intake of proton pump inhibitors (PPI), Crohn's disease, malignancy, coagulopathies, and esophageal varices. These patients underwent gastroduodenoscopy and esophageal biopsies,obtained from both the upper and lower esophagus and visible abnormal mucosa. EoE was diagnosed if number of mucosal eosinophils was more than fifteen per high-power field.

Results: Prevalence of EoE was 1.88%. Both patients with EoE were male with median symptom duration of 9 months. Both had retrosternal pain, one had history of dysphagia, food impaction and heart burn. A history of allergy was noted in 1 (50%). Median absolute eosinophil count was 525/mm^3 versus non EoE 134. Combination of all four clinical features reached statistical significance (p=0.0001). Patients with EoE had more history of allergy (50% vs 8.6% p=0.45), higher median absolute eosinophil count (525 vs 134, p=0.12) and lower response to PPI (51% vs 0%, p=0.31) on univariate analysis but not in multivariate analysis.

Conclusions: The prevalence of EoE was found to be low (1.88 %). Male sex, combination of above mentioned clinical features suggest EoE. Personal histories of allergy, endoscopic esophagitis, absolute eosinophil count and non response to PPIs are not significant predictors of EoE.

Keywords: Eosinophilic esophagitis, Prevalence, Esophageal symptoms

INTRODUCTION

Eosinophilic esophagitis (EoE) has recently evolved as a distinct chronic inflammatory disease of esophagus, both in children and in adults, with increasing prevalence all over the world[1]. It is now appreciated that many disorders are accompanied by eosinophil infiltration in the esophagus: EoE, eosinophilic gastroenteritis, gastroesophageal reflux disease (GERD), parasitic and fungal infections, inflammatory bowel disease (IBD), hypereosinophilic syndrome (HES), esophageal leiomyomatosis, myeloproliferative disorders, carcinomatosis, polyarteritis, allergic vasculitis, collagen vascular diseases (e.g., scleroderma), pemphigus vegetans, and drug injury[2]. Its diagnosis is based on characteristic clinical symptoms such as heartburn, vomiting, chest pain, dysphagia, and histological finding of presence of mucosa infiltrating eosinophil-predominant inflammation, once the other causes of mucosal eosinophilia are excluded[3]. Clinically, the diagnosis of EoE is difficult to suspect, as its manifestations mimic with those having other esophageal disorders, such as gastroesophageal reflux disease (GERD). In 2011, a working group proposed a new conceptual definition for EoE as an immune/antigen mediated esophageal disease characterised clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation[4]. Although proton pump inhibitor (PPI) responsiveness would not violate this definition, the EoE working group nevertheless recommended in their diagnostic guidelines that PPI- responsive esophageal eosinophilia should be excluded to establish a diagnosis of EoE but these guidelines have been revised recently and PPI- responsive esophageal eosinophilia is no longer an exclusion[4,20].

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Also there is growing consensus that antigen- mediated EoE can respond to PPIs irrespective of the presence of detectable GERD[5]. The clinical manifestations of EoE vary with different age of presentation[1, 6-8]. Approximately 1% to 9% of patients with symptoms of GERD have been reported to have EoE[9-10]. EoE annual incidence rates vary between 0.1 and 1.2 per 10,000 in several studies, with EoE representing the second most common cause of chronic esophagitis[10, 11]. There is paucity of data regarding the prevalence of EoE in Indian patients having various esophageal symptoms. Prasad et al. reported 10% to 15% prevalence of EoE in patients with dysphagia[12]. In another study by Veerappan et al, on 400 consecutive patients undergoing esophagogastroduodenoscopy for various indications, EoE was identified in 6.5% cases[13]. Other prospective studies found comparable prevalence of EoE, ranging between 2.4% and 6.6%[14–17]. One study from north india showed prevalence of EoE in patients with GERD was 3.2%[18]. So we planned a study to screen consecutive patients having esophageal symptoms for presence of EoE.

AIM: Aim of our study was to assess the prevalence of eosinophilic esophagitis in adult patients with esophageal symptoms at a tertiary care centre in north-west part of India.

MATERIALS AND METHOD

This was a prospective observational study. We screened adult patients with esophageal symptoms presenting to Gastroenterology OPD at our institution, between April 2019 to March 2020. We included patients with retrosternal discomfort, heartburn, dysphagia to solids and history of food bolus impaction for at least 4 weeks and who consented for the esophago-gastroduodenoscopy examination and biopsy. We excluded patients with a previous/current diagnosis of infectious esophagitis, recent intake of PPI (with in 4 weeks), Crohn's disease, esophageal malignancy, patients with known history of coagulopathy, thrombocytopenia and esophageal varices. The patients fulfilling above criteria underwent gastroduodenoscopy and esophageal biopsies (six to eight), obtained from both the upper esophagus (five cm below the upper esophageal sphincter [three bx at least]) and lower esophagus (five cm above gastroesophageal junction [three bx at least]), as well as from any other endoscopically visible abnormal mucosa[18]. Demographic and clinical characteristics, endoscopic findings, peripheral blood film with eosinophilic count, Anti Nuclear Antibodies (ANA), Prothrombin time with International Normalised Ratio, presence of related co-morbidities (asthma, atopic dermatitis, etc.), duration of PPI use, and response to PPI were also recorded. Response to PPI was considered when a patient had at least 50% symptomatic improvement after at least 2 weeks of PPI therapy using visual analogue scale to assess response.

The typical endoscopic findings of EoE include edema (decreased vasculature, pallor), exudate (superficial white specks coating the mucosa), furrowing (linear lines, longitudinal to the esophageal axis), concentric rings ("trachealization"), and strictures.

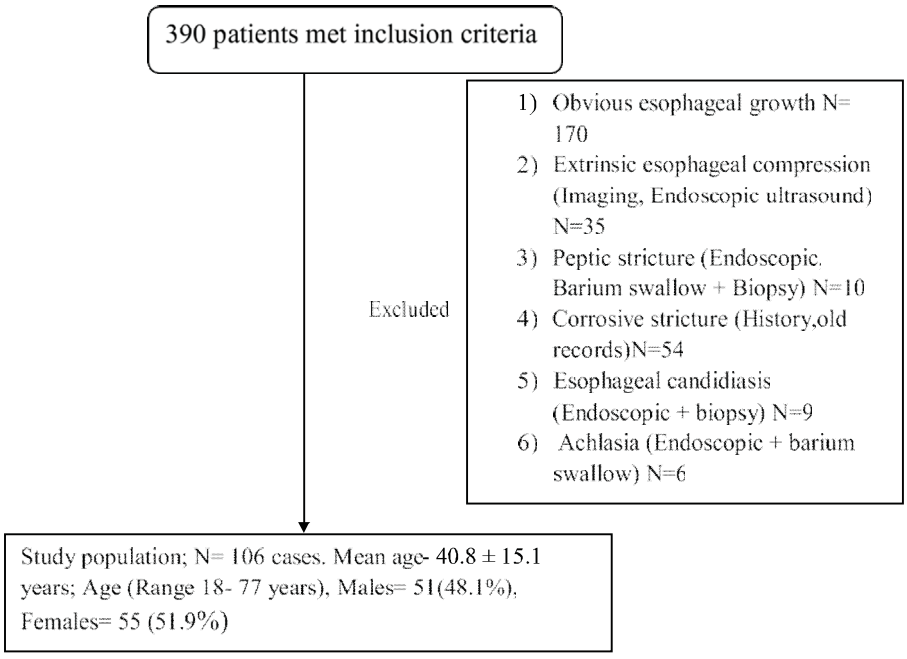

Figure1. Study population

Stool examination was done to rule out parasitic infections. Two experienced pathologists interpreted the biopsies independently and thereafter reached to a conclusive result after discussion. Presence or absence of features of reflux esophagitis, presence or absence of eosinophil, evidences of eosinophil degranulation, presence of parasites, sub-epithelial stromal changes, and presence or absence of epithelial dysplasia or malignancy were noted in all the biopsies. The number of eosinophils per high-power fields was recorded, based on averaged eosinophil count in all the biopsy fragments. EoE was diagnosed if number of mucosal eosinophil infiltrate was more than fifteen per high-power field[3].

Statistical analysis Qualitative data and quantitative data were analyzed using chi-square and t test, respectively. Univariate analysis of various factors was carried out to determine independent predictors of EoE in patients with various esophageal symptoms.

RESULTS

390 consecutive patients fulfilling inclusion criteria were screened and on endoscopy and other relevant investigations such as barium swallow. The results were; obvious esophageal growth (170), extrinsic esophageal compression (35), peptic stricture (10), corrosive stricture (54), esophageal candidiasis (9) and achlasia (6) and these were excluded.

106 patients were included as study subjects [Figure 1]. Mean age of the study subjects was 40.8 ± 15.1 years (Range 18- 77 years). 51 patients (48.1%) were men and 55 (51.9%) were females. Median duration of symptoms was 7 months (Range 2-24 months). 14 (13.2%) were smoker, 10 (9.4%) were oral tobacco users and 18 (17%) were chronic ethanol users. Previous intermittent use of PPI was present in 72 patients. Symptoms were retrosternal pain (75.47%), heart burn (52.8%), dysphagia (20.75%) and food bolus impaction (0.9%). A personal history of allergy was seen in 10 patients (9.4%). Response to PPI was seen (with omeprazole 20 mg twice daily for 2 weeks) in 53 patients (50%). Stool microscopic examination revealed presence of giardia cysts in the stool in 6 patients (5.66%). Human immunodeficiency virus (HIV) testing was done in all the patients; none of them had a positive test. The overall median absolute eosinophil count in this cohort was 134 (43–1500). At our institution, the upper limit of peripheral eosinophil count is considered as 400/mm^3. Patients who had severe or complete dysphagia were auto excluded and underwent endoscopy as soon as feasible, other underwent endoscopic procedure after 6 weeks (PPI twice daily for first 2 weeks to see PPI response and stoppage of PPI, 4 weeks prior to endoscopic procedure) and those with response were shifted to H2 receptor blockers (ranitidine 150 mg bd) to exclude PPI responsive esophageal eosinophilia. Forty one (38.6%) patients had normal findings on endoscopic examination. 64 (60.4%) patients had features of esophagitis in accordance with Los Angeles classification[19] [LA-A in 32 (30.18%), LA-B in 25 (22.64%), LA-C in 3 (2.8%) and LA-D in 4 (3.77%). One patient (0.9%) showed trachealization of the esophagus with esophageal rings and linear esophageal furrows (Table 1). The patient with trachealization of the esophagus was later diagnosed to have EoE based on histology. One patient (0.9%) with esophagitis was also later diagnosed to have EoE.

Prevalence of EoE in patients with esophageal symptoms:

Esophageal biopsy revealed significant eosinophilia of more than 15/high-power field in 2 of 106 patients with esophageal symptoms. The mean peak eosinophil count in EoE patients was 75/HPF (Range 60-90). Eosinophilic infiltration was seen in both proximal and distal sites of esophaus in both patients. Eosinophilic abscess were found in one patient; superficial layering, basal zone hyperplasia and dilated intercellular spaces in both the patients. So, the prevalence of EoE was 1.88%. Both the patients with EoE were male and the median duration of symptoms in them were 9 months (range 6 to 12 months). Both the patients had retrosternal pain, while one had dysphagia, history of foreign body impaction and heart burn. A history of allergy was noted in 1 (50%) of them. Median absolute eosinophil count was 525/mm^3 (range 160-890) in comparison to those without EoE [134 (range 43–1500)/mm3]. While they were on PPI, none had response to this medication compared with 51% response in those without EoE. Stool microscopic examination of both the patients was normal (Table 1).

Predictors of EoE in patients with esophageal symptoms:

Combination of clinical features (retrosternal pain, heart burn, dysphagia to solids and food bolus impaction) reached statistical significance in patients with EoE versus those without it (p=0.0001). Patients with EoE had more history of allergy (8.6% vs. 50%, p=0.45), higher median absolute eosinophil count (525 vs 134 p=0.12) and lower response to PPI (0% vs 50%, p=0.31) on univariate analysis, but none of these result reached statistical significance (Table 2).

Table 1. Baseline Characteristics of Patients with Esophageal Symptoms

Baseline characteristics	All patients with esophageal symptoms N=106	Patients with esophageal symptoms without EoE N=104	Patients with esophageal symptoms EoE N=2
Mean age (± SD) in years	40.8 ± 15.1	40.7 ± 15.19	51 ± 7
Males Females Median duration of symptoms (Range)	51 (48.1%) 55 (51.9%) 7 (2-24 months)	49 (47.12%) 55 (52.88%) 7 (2- 24 months)	2 (100%) 0 9 (6-12 months)
Symptoms Retrosternal pain Heart burn Dysphagia to solids Food bolus impaction	 80 (75.47%) 56 (52.8%) 22 (20.75%) 1 (0.9%)	 76 (73.07%) 55 (53.7%) 21 (20.2%) 0	 2 (100%) 1 (50%) 1 (50%) 1 (50%)
Response to PPI	53 (50%)	53 (51%)	0
History of allergy	10 (9.4%)	9 (8.6%)	1 (50%)
Median absolute eosinophil count (Range)	141 (43-1500)	134 (43-1500)	525 (160-890)
Endoscopic findings a)Normal b)Esophagitis LA grade A c)Esophagitis LA grade B d)Esophagitis LA grade C e) Esophagitis LA grade D f)Trachealization of esophagus with rings and Linear esophageal furrows	 41 (38.6%) 32 (30.18%) 25 (22.64%) 3 (2.8%) 4 (3.77%) 1 (0.9%)	 41 (39.42%) 32 (30.76%) 24 (23.07%) 3 (2.88%) 4 (3.8%) -	 - - 1 (50%) - - 1 (50%)

Table 2: Predictors of Eosinophilic Esophagitis in Patients with Esophageal Symptoms- Univariate Analysis

	Without EoE (N=104)	With EoE (N=2)	P value
History of allergy Yes No	 9 (8.65%) 95 (91.35%)	 1(50%) 1 (50%)	0.45
Response to PPI Yes No	 53 (51%) 51 (49%)	 - 2 (100%)	0.31
Symptoms Retrosternal pain Heart burn Dysphagia to solids Food bolus impaction	 76 (73.07%) 55 (53.7%) 21 (20.2%) 0	 2 (100%) 1 (50%) 1 (50%) 1 (50%)	0.0001
Absolute eosinophil count (Median)	134	525	0.12

DISCUSSION

In the present study, the prevalence of EoE in patients with esophageal symptoms was 1.88% which was similar to the study conducted by Baruah et al, which is study in GERD patients for prevalence of EoE[18]. MK Joo et al, in patients with upper gastrointestinal or esophageal symptoms had shown the prevalence of EoE to be 6.6%[15], which is higher than reported by us. In another study by Veerappan et al, on 400 consecutive patients undergoing esophagogastroduodenoscopy for various indications, EoE was identified in 6.5% cases[13]. If we include all patients undergoing esophago-gastroduodenoscopy at our centre for esophageal symptoms, the prevalence of EoE was 0.51% (2 out of 390 in one year), suggesting that EoE is a uncommon disease in North- west part of our country. We did not find history of allergy, nonresponse to PPI and eosinophil count to be predictors for EoE. These factors were shown to be predictors for EoE in the study by Baruah et al[18]. Rather we found that presence of combination of clinical features of retrosternal pain, heart burn, dysphagia to solids and food bolus impaction accurately predict EoE. We found retrosternal pain in 100%, heart burn in 50%, dysphagia in 50% and food bolus impaction in 50% patients with EoE which is quite similar to study by MK Joo et al[15]. Similar to their study and study by Veerappan et al[13], we found EoE to be male predominant. Mean age in our patients with EoE was 51 ± 7 years, which was similar to studies by Zink DA et al and Baruah et al[17,18]. The classic endoscopic findings in patients with EoE described include multiple esophageal rings, longitudinal furrows, whitish plaques and strictures. In the prospective study by Veerappan et al., the majority of EoE patients (72%) had one of these findings[13]. Similarly MK Joo et al had shown these endoscopic features in 75% of patients with EoE. We also found that one of our patients with EoE had trachealization of esophagus with rings and linear esophageal furrows. In the present study, out of the 64 patients having endoscopically documented esophagitis, 1 (1.5%) had EoE which was quite lower than 14.7% as described by Baruah et al[18].

In summary, the prevalence of eosinophilic esophagitis in patients with esophageal symptoms was found to be 1.88 % which is quite low.

Combination of clinical features of retrosternal pain, heart burn, dysphagia and food bolus impaction can suggest eosinophilic esophagitis. Personal histories of allergy, presence of endoscopic esophagitis, absolute eosinophil count and nonresponse to PPIs are not significant associated risk factors for presence of EoE.

There are several limitations in our study. First, we did not routinely perform a random biopsy at the stomach and duodenum to exclude eosinophilic gastroenteritis. However, we performed a gastric or duodenal biopsy in 4 patients who had edema, erythema, hemorrhage and/or erosions in these areas, and two were found to have eosinophilic duodenitis, but their esophageal biopsies did not reveal EoE. Secondly, we could not perform a 24 hour pH monitoring study of distal esophagus to exclude abnormal acid reflux as this facility is not available at our institute. However, both EoE patients were unresponsive to PPI therapy and this might distinguish GERD from EoE. The study was single centric and may be suffering for referral bias, also the possibility of long term remission of disease by previous PPI use is a distinct possibility. The actual number of EoE is only two, hence a very large multicentre study only can resolve these discordant findings.

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