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A study on eosinophilic and Lymphocytic esophagitis in patients with typical gastroesophageal reflux disease symptoms

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Abstract---Background: Eosinophilic esophagitis (EoE) has emerged as an important gastrointestinal (GI) disorder during the last 15 years, affecting approximately 15% of patients with dysphagia EoE presents a diagnostic challenge because eosinophils are also a feature of acid-induced esophagitis. The aim of this study was to evaluate prospectively the presence of eosinophilic and lymphocytic esophagitis in patients with typical gastroesophageal reflux disease symptoms. Patients and Methods: This was a prospective study which was conducted on 200 patients, to estimate the prevalence of eosinophilic and lymphocytic esophagitis in patients with typical gastroesophageal reflux disease symptoms. Results: Regarding serum IgE as laboratory investigation, all the cases 6 (100%) diagnosed to have EoE showed elevated level of serum IgE level ((normal range was used according to the laboratory was: 0 – 165 IU/ml). There was statistical significance for the presence of elevated serum IgE level and peripheral serum eosinophilia between positive and negative cases for EoE Conclusion: Eosinophilic esophagitis is not uncommon disease and presented in 6 cases out of 200 patients having typical symptoms of GERD. All the positive EoE cases having history of allergy and most of them are asthmatic. Eosinophilic esophagitis is considered as a possible cause of refractory GERD, most of our EoE were having refractory GERD

symptoms. EREFS is a good tool to characterize endoscopic findings of EoE. Both proximal and distal esophageal biopsies are important to diagnose eosinophilic esophagitis with distal biopsies are mandatory for diagnosis.

Keywords---eosinophilic esophagitis, gastroesophageal reflux, lymphocytic, gastrointestinal.

Introduction

Eosinophilic esophagitis (EoE) also known as “asthma of the esophagus” is a chronic immune/antigen mediated disorder of the esophagus affecting both children and adults. It is a clinicopathologic disease characterized clinically by dysphagia and pathologically by esophageal eosinophilia. Diagnosis is made by 3 criteria: (1) symptoms of esophageal dysfunction; (2) presence of ≥ 15 eosinophils/high power field in at least 1 esophageal biopsy; and (3) eosinophilia limited to the esophagus, with exclusion of other possible causes of esophageal eosinophilia, including proton pump inhibitors (PPI) responsive esophageal eosinophilia (1).

The disease is increasingly being recognized over the last few decades. The prevalence of EoE is currently as high as 50 patients per 100000 population in the United States and Europe (2). The disease can affect both children and adults. In adults, it mostly affects middle aged men between the age of 30 and 50. Most of the patients with eosinophilic esophagitis have personal history of allergic disorders like bronchial asthma, allergic rhinitis, allergic conjunctivitis or food allergy (3).

Exposure of the esophagus to food and aeroallergens in genetically predisposed individuals may initiate the process of eosinophilic esophagitis although the exact mechanism is currently unknown. Foods most commonly implicated in EoE are: Milk, egg, wheat, soy, peanuts, beans, rye and beef (4). More than one allergen or immune mechanism may contribute to this disease and therefore therapies may not only have to be individualized but also be acceptable to patients since long-term therapy may be necessary in order to avoid sub-epithelial fibrosis and remodeling of the esophagus (5).

The major features include infiltration of numerous eosinophils (usually > 15 per high power field) into the squamous epithelium, layering of eosinophils on the surface layer and eosinophilic microabscess formation (clusters of ≥ 4 eosinophils). Often necrotic squamous cells are also seen on the surface layer (6). Minor features include chronic inflammatory infiltrate into the lamina propria with fibrosis of the lamina propria, hyperplasia of muscular layers and basal epithelial cells with lengthening of lamina propria papillae, and intercellular edema (7).

Treatment options for LyE have not been well studied or defined. Given one of the main symptoms of LyE being heartburn, proton pump inhibitors (PPI) have been prescribed to patients. One study found that about half of patients diagnosed

with LyE felt improvement of their initial symptoms after starting a PPI, although it was unsure if there was concomitant GERD that was being treated (8).

Patients and Methods

This was a prospective study which was conducted on 200 patients, to estimate the prevalence of eosinophilic and lymphocytic esophagitis in patients with typical gastroesophageal reflux disease symptoms. The study was carried out in the period from January 2014 till January 2016, in Theodor Bilharz Research Institute (TBRI) Giza, Egypt (total number of patients were 67) and King Abdullah Medical City (KAMC) Makkah, Saudi Arabia (Total no of patients 133). Ethical approval was obtained from the TBRI-Institutional Review Board (IRB) and from the Ministry of Scientific Research and KAMC official departmental agreement. Informed consents were obtained from all patients recruited in the study.

Inclusion criteria: Patients with age ranging from 17 – 70 years, with typical gastroesophageal reflux disease symptoms candidate for upper GI endoscopy.

Exclusion criteria: Patients with a previous history of upper digestive tract surgery, patients with decompensated chronic diseases and / or malignancy, patients with a previous upper digestive endoscopy showing active Peptic ulcer, esophageal diverticulum, Barrett's esophagus, patients taking corticosteroids and patients refusing to undergo the procedure or accepting the consent.

Methodology

All patients were subjected to

Clinical assessment, including:

1. Full history taking: Stressing on GERD symptoms which were divided into typical and atypical symptoms. Typical symptoms include: heart burn, acid regurgitation. Atypical symptoms include: throat cleaning, otitis media, hoarseness of voice, chronic cough and nocturnal asthma. History of previous treatment for H.pylori, history of allergy, asthma, atopic dermatitis and IBD and surgical history especially gastric or esophageal surgeries.
2. Clinical examination: General examination and abdominal examination for the liver, spleen & the presence of ascites.

Laboratory Investigations: Complete blood picture (to detect peripheral eosinophilia or lymphocytosis), serum IgE (normal reference range used was 0 - 165 IU/ml), liver profile: Alanine transaminase (ALT), Aspartate transaminase (AST), alkaline phosphatase (ALP), Serum bilirubin (direct and indirect) and serum albumin, renal function tests: Serum urea and creatinine and stool analysis to rule out parasitic infestation.

Upper GI Endoscopy: Patients came to the endoscopy unit after an overnight fasting. Each patient was given intravenous sedation with midazolam and/ or propofol, in a titrated dose before the endoscopy. Careful explanation of the procedure to the patient, including risks and benefits were given, with informed and written consent for the procedure were taken before the procedure. The Eosinophilic esophagitis Endoscopic Reference Score (EREFS) was used for

assessment for the previous recorded endoscopic findings during examination. This acronym stands for the five main findings: Exudates, Rings, Edema, Furrows, and Strictures (9). Utilization of this newly validated classification and grading system for endoscopic findings of EoE may improve diagnostic utility. This system allows for more uniform characterization of endoscopic findings, facilitates comparisons of severity among clinicians, and provides information regarding fibrostenotic complications of EoE (9).

Esophageal Biopsies: Biopsies were taken from all patients 5cm (lower esophagus) and 10 cm (upper esophagus) from the esophageal-gastric junction (10). The biopsies were preserved in 10% formalin till examined. Two samples were collected from each site, and one extra sample was taken when mucosal alterations were observed. Other two stomach biopsies (antrum) were taken to rule out eosinophilic gastroenteritis (11). Testing for H.pylori was done during endoscopic examination using CLO test (rapid urease test) and was considered positive or negative according to the test reference.

Histopathology: Intraepithelial eosinophils and lymphocytes were counted in up to six high-power fields (hpf: 0.158 mm²) (x400) after hematoxylin/ eosin staining. **Specimen/Biopsy Processing:** Biopsy is placed in cassette, tissue embedded in paraffin with proper orientation, tissue is cut with microtome at 4-5 microns, and then it is placed on a glass slide and stained. A diagnosis of eosinophilic esophagitis was established when the number of intraepithelial eosinophils in the esophagus was equal and/or more than 15 EO/HPF (12) in at least one HPF at any level of the esophagus. A diagnosis of lymphocytic esophagitis was established if the biopsies had a high number of intraepithelial lymphocytes and the presence of a dense peripapillary lymphocytic infiltrate and peripapillary spongiosis involving the lower two-thirds of the esophageal epithelium and the absence of significant neutrophilic or eosinophilic infiltrates (13).

Patients follow up: Patients who were diagnosed to have EoE were followed up regularly in the outpatient clinic. Patients attended three appointments and informations were collected from them about their symptoms, adherence and response to therapy trying to characterize the natural history of the disease and relation of the EoE specific symptoms in comparison to GERD symptoms and if any link to refractory GERD cases diagnosed before.

Statistical Analysis: Results are expressed as mean \pm standard deviation or number (%). Comparison between categorical data [number (%)] was performed using either Chi square test or Fisher exact test whenever it was appropriate. Comparison between variables in the two groups was performed using unpaired t test. Statistical Package for Social Sciences (SPSS) computer program (version 19 windows) was used for data analysis. P value \leq 0.05 was considered significant.

Results

This study was conducted on 200 patients, to estimate the presence of eosinophilic and lymphocytic esophagitis in patients with typical gastroesophageal reflux disease symptoms. The study was carried out in the period from January 2014 till January 2016, in Theodor Bilharz Research

Institute (TBRI) Giza, Egypt (total number of patients were 67) and King Abdullah Medical City (KAMC) Makkah, Saudi Arabia (Total no of patients 133).

Table (1): Demographic features of all the studied patients (n=200)

	Number	percent
Age (yrs.)		
Minimum-maximum	19 - 70	
Mean \pm SD	50.11 \pm 11.63	
Sex		
Female	75	37.5
Male	125	62.5
Residence (yes)		
Egyptian	67	33.5
Saudi	133	66.5

The mean age \pm SD of the studied group was (50.11 \pm 11.63) with male predominance in our patients representing 125 (62.5%) patients and most of the patients were Saudi 133(66.5). Table (1)

Table (2): Different endoscopic grades of endoscopically proved GERD in comparison between refractory and non-refractory GERD cases

	Non-refractory (n= 100)	Refractory (n= 19)	p value
GERD A	67 (67%)	11 (57.9%)	0.347
GERD B	20 (20%)	7 (36.8%)	
GERD C	8 (8%)	1 (5.2%)	
GERD D	5 (5%)	0 (0.0%)	

Data are expressed as number (%). $p > 0.05$ = not significant.

Regarding GERD symptoms in correlation to PPI therapy and according to the definition, 32 (16%) patients were classified to have refractory GERD. Regarding the endoscopic findings of GERD (different Los Angeles classifications) among these refractory patients, 19 (59.3%) patients had erosive esophagitis and grade A esophagitis was the most predominant endoscopic GERD finding which was found in 11 cases (57.9%) in comparison to 13 (40.6) cases having normal endoscopy. This means that refractory GERD cases may have either normal or evidence of mucosal breaks during endoscopic examination. Regarding different grades of reflux esophagitis (according to Los Angeles GERD classification) in comparison between refractory and non-refractory cases, there was no statistical significant difference between the two groups. Table (2)

Table (3): Histopathological results of the studied patients (n=200)

	Number	percent
Upper esophageal biopsies		
Normal	194	97.0
Compatible for EoE	4	2.0

Reflux Esophagitis	2	1.0
Lower esophageal biopsies		
Normal	54	27.0
Compatible for EoE	6	3.0
Reflux esophagitis	135	67.5
Reflux esophagitis + intestinal metaplasia	5	2.5
Antral biopsies		
Normal	167	83.5
Chronic gastritis	19	9.5
Chronic gastritis + <i>H. pylori</i>	8	4.0
No eosinophilis	200	100%

Data are expressed as number (%).

Regarding esophageal biopsy results of the cases positive for EoE (6 cases), 4 (66.6%) cases showed typical features of EoE histologically from upper esophageal biopsies and all the cases 6 (100%) cases showed typical features of EoE (eosinophil count were more than 15 Eo/hpf) from the lower esophageal biopsies. From the upper esophageal biopsies two (2%) cases showed evidence of reflux esophagitis histologically and from the lower esophageal biopsies 135 (67.5%) patients showed evidence of reflux esophagitis. Five (2.5%) cases from all the cases (200) were diagnosed to have intestinal metaplasia from the lower esophageal biopsies with no evidence of dysplasia or carcinomatous deep invasion and these cases were given follow up and endoscopic surveillance according to the international guidelines. Regarding antral biopsies (which were taken to rule out eosinophilic gastroenteritis by the presence of eosinophilic gastric infiltration), among the cases positive for EoE (6 cases), antral biopsies showed no evidence of eosinophilic infiltration and also rest of the cases (-Ve EoE) there was no eosinophilic infiltration. So in our study no evidence of eosinophilic infiltration outside the esophagus was noticed. 167 (83.5%) cases showed normal histological findings, 19 (9.5%) cases showed histological features of chronic gastritis, and 8 (4%) cases showed histological features of chronic gastritis and were positive for *H. pylori*. Table (3)

Table (4): Serum IgE level among the positive cases for eosinophilic esophagitis (EoE) (n=6)

	Number	percent
Serum IgE		
Normal	0	0.0
Elevated	6	100.0

Regarding serum IgE as laboratory investigation, all the cases 6 (100%) diagnosed to have EoE showed elevated level of serum IgE level ((normal range was used according to the laboratory was: 0 – 165 IU/ml)). Table (4)

Table (5): comparison of serum IgE and peripheral eosinophilia between positive and negative EoE cases

	Negative EoE (n= 194)	Positive EoE (n= 6)	p value
Serum IgE			
Normal	194 (100.0%)	0 (0.0%)	0.001*
Elevated	0 (0.0%)	6 (100.0%)	
Peripheral eosinophilia positive	2 (1.0%)	3 (50.0%)	0.001*

Data are expressed as number (%). *p< 0.05= significant.

There was statistical significance for the presence of elevated serum IgE level and peripheral serum eosinophilia between positive and negative cases for EoE. Table (5)

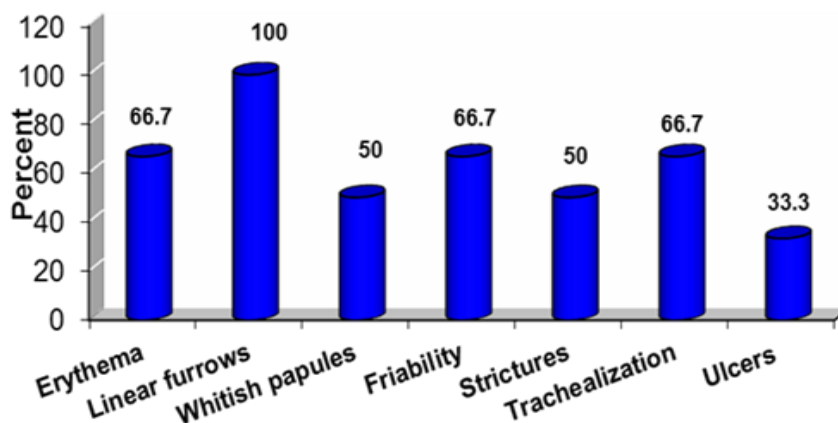


Figure (1): characteristic endoscopic findings among the positive cases for eosinophilic esophagitis

During endoscopic examination and considering the characteristic endoscopic findings were observed among the cases positive for EoE, linear furrows were present in all cases of positive EoE 6 (100%) cases, Erythema was found in 4 (66.7%), whitish papules were seen in 3 (50%) cases, friability was seen in 4 (66.7%) cases, strictures were observed in 3 (50 %) cases, trachealization was seen in 4 (66.7%) cases and ulcers were the least endoscopic finding to be seen and was noticed in 2 (33.3%) cases. Figure (1)

Table (6): comparison of Endoscopic findings between positive and negative cases of EoE in the studied patients

	Negative EoE (n= 194)	Positive EoE (n= 6)	p value
Erythema	0 (0.0%)	4 (66.7%)	0.001
Linear furrows	0 (0.0%)	6 (100.0%)	0.001

Whitish papules	0 (0.0%)	3 (50.0%)	0.001
Friability	0 (0.0%)	4 (66.7%)	0.001
Strictures	4 (2.1%)	3 (50.0%)	0.001
Trachealization	0 (0.0%)	4 (66.7%)	0.001
Ulcers	2 (1.0%)	2 (33.3%)	0.001

Data are expressed as number (%). * $p < 0.05$ = significant.

The previous data regarding comparison of presence of special Endoscopic findings between positive and negative cases of EoE is showing statistically significant difference between positive and negative cases of EoE regarding the presence of erythema, linear furrows, whitish papules, friability, strictures, trachealization and ulcers. The Eosinophilic esophagitis Endoscopic Reference Score (EREFS) was used for assessment for the previous recorded endoscopic findings during examination and the results were as follow: EREFS classification system for the positive cases in our study was as follow: Case no (one): E0 R1 E1 F1 S0, Case no (two): E1 R1 E1 F1 S1, Case no (three): E1 R1 E1 F1 S1, Case no (four): E0 R0 E1 F1 S0, Case no (five): E1 R1 E0 F1 S1 and Case no (six): E0 R0 E0 F1 S0. Table (6)



Figure (2): Endoscopic picture for one patient showing linear furrows and mucosal edema: E0 R0 E1 F1 S0



Figure (3): Endoscopic picture for one patient showing esophageal trachealization (rings): E0 R1 E1 F1 S0

The above two figures showing the endoscopic appearance of two cases from our diagnosed eosinophilic esophagitis cases in our study, showing the special characteristic endoscopic findings were seen with applying the EREFS scoring system.. Figure (2, 3)

Typical histological features of eosinophilic esophagitis which was noticed and reported by the histopathologist were as follows: All cases were showing esophageal mucosal eosinophilic count above 15 per hpf and this was considered by the histopathologist to be diagnostic for EoE All the cases showed basal cell hyperplasia, dilated intercellular spaces, elongation of vascular papillae and intercellular edema. Two cases (33.3%) had eosinophilic microabscesses. Figure (4)

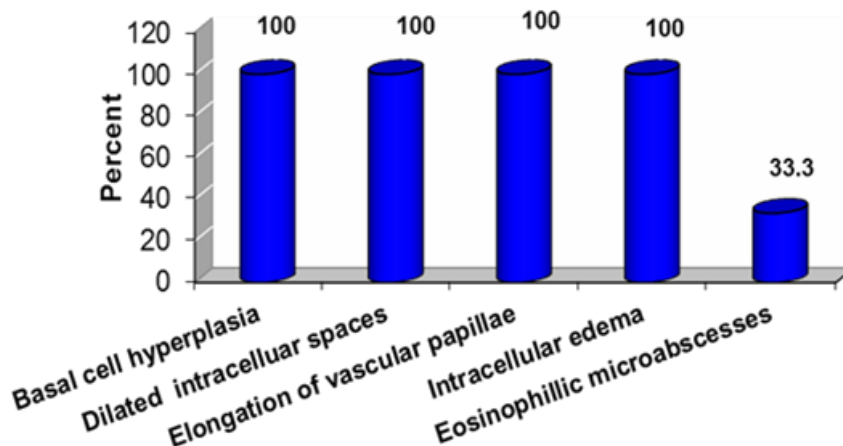


Figure (4): Special histological characters among the positive cases for eosinophilic esophagitis

Discussion

Eosinophilic esophagitis (EoE) has emerged as an important gastrointestinal (GI) disorder during the last 15 years, affecting approximately 15% of patients with dysphagia EoE presents a diagnostic challenge because eosinophils are also a feature of acid-induced esophagitis, especially in children (14). In our study we tried to estimate the presence of eosinophilic and lymphocytic esophagitis in patients with typical gastro esophageal reflux disease symptoms and to through light its real prevalence especially we conducted this study in two different communities. We recruited in this study 200 patients who have typical symptoms of GERD and were candidate for upper endoscopy.

In our study we found that typical GERD presentation was present in 90.5% of patients and 9.5% of patients were presenting with atypical beside the typical symptoms of GERD. In patients who were presenting with typical symptoms of GERD, heart burn was the main symptom of presentation followed by acid regurgitation. Regarding the atypical symptoms presentation of GERD, throat cleaning was the most prevalent symptom (12 cases 6.0%) hoarseness of voice in (5 cases 2.5%) then chronic cough (4 cases 2%).

This is in agreement with DeVault et al., (15) who reported that heartburn is the classical symptom of GERD and the other common symptom of GERD is acid regurgitation. Vakil et al., (16) reported that Heartburn and regurgitation are the typical symptoms of GERD, but GERD can also manifest itself through non-cardiac chest pain, pulmonary or ear, nose and throat symptoms and dental erosion. Our results of percentage of prevalence of atypical symptoms were not matching with Jaspersen et al., (17) who stated that chronic cough is one of the most common clinical presentations in primary care practice, it is believed that cough is common in both erosive (30.5%) and nonerosive (34.9%) GERD. The major limitation of many of these studies regarding the true prevalence of chronic cough as an atypical symptom of GERD is that patients with reflux-associated cough may have silent GERD and not showing any GERD symptoms.

Final results of our study showed that total cases diagnosed with EoE were 6 cases and we found EoE was more prevalent in male patients (4 cases 66.7%) than females (2 cases 33.3%). This is in agreement with Straumann et al., (18) who stated that The majority of affected adults have been men and these findings may be related to variations in a gene located on the X-chromosome that have been associated with eosinophilic esophagitis. In some reports the incidence in males is even as high as 86% of patients (19).

We included in our study patients with age ranging from 17 to 70 years and the age distribution for cases positive for EOE was ranging from 19 to 37 with mean age \pm SD was (28.83 \pm 6.65). In our study pediatric age group was not included. These data are compatible with Straumann et al., (18) who stated that the majority of affected adults have been men in their 20s or 30s, although later presentations have been described. In a series of 31 adults (24 men and 7 women), the mean age at diagnosis was 34 years (20). This also was noticed by Potter et al., (21) who mention that in adults, eosinophilic esophagitis can present in the third or fourth decades of life and various studies implicate it to be more predominant in men.

We conducted our study on two different communities and our data showed that from EoE positive cases, 2 cases were Egyptian and 4 were Saudi. A study done in Saudi Arabia to differentiate the presence of EoE between developed and developing countries, Al-Hussaini et al., (22) conducted their retrospective study to identify all patients who were diagnosed in their institution with EoE from April 2004 to December 2011.their results showed 45 patients were diagnosed with EoE (37 children and 8 adults; 36 males; median age 10.5 years, range from 1–37 years). They concluded that EoE is increasingly recognized in Saudi Arabia.

The data from our study showed that 5 patients from the positive EoE cases (6 cases) according to the definition (symptoms history and PPI response) were classified to have refractory GERD and this represent 15.6% from the total cases of refractory GERD (32 cases), this means that cases with refractory GERD should be evaluated for possibility of presence of eosinophilic esophagitis which considered to be not uncommon among these group of patients.

Our data were more prevalent than the data revealed by a study done in Egypt by Mohamed El Malatawy et al., (23) who investigated cases with refractory GERD (40 cases) for the presence of EoE, their conclusion was that The prevalence of

eosinophilic esophagitis was 2.5% (1/40). This difference may be explained that in their study only cases with refractory GERD were included, in our study refractory and non-refractory GERD cases were enrolled. García-Compeána et al., (24) concluded that EoE is an uncommon condition (4%) in patients with refractory symptoms of GERD (but they diagnose EoE based on eosinophil count at least 20 eosinophils×high power Field). Results of a study done by Claudia Cristina et al., (25) demonstrated a low prevalence of EoE among patients with refractory GERD undergoing omeprazole treatment. Among the 103 studied patients only one patient presented with lesions suggestive of EoE

During endoscopic examination and considering the characteristic endoscopic findings were observed among the cases positive for EoE, linear furrows were present in all cases of positive EoE 6 (100%) cases, followed by erythema, friability and trachealization. Strictures and ulcers were the least common endoscopic findings. The Eosinophilic esophagitis Endoscopic Reference Score (EREFS) was used for assessment for the previous recorded endoscopic findings during examination. There was statistically significant difference between positive and negative cases of EoE regarding the previous mentioned endoscopic findings. Regarding EREFS system a study by Rhijn et al.,(26) has provided the first external validation of the EREFS system with the objective of unifying the endoscopic description of EoE.

Our data were similar to the data from a study done by Mulder et al., (27) who revealed that four endoscopic features were significantly different between patients with EoE and age-matched patients with GERD. Trachealization, linear furrows, and white papules were significantly more likely to be found in the patients with EoE and a normal endoscopic appearance was more likely to be found in patients presenting with GERD. Regarding the histopathological results in our study, All EoE positive cases showed esophageal mucosal eosinophilis count above 15 per hpf. For the other histological characters, all the cases showed basal cell hyperplasia, dilated intercellular spaces, elongation of vascular papillae and inter cellular edema. Two cases (33.3%) had eosinophilic microabscesses. We took about 4 to 6 biopsies from each patient (proximal and distal esophagus). Four cases were diagnosed from proximal esophageal biopsies and the six cases diagnosed from distal esophageal biopsies and these findings highlight the importance of both proximal and distal esophageal biopsies with more stressing on the distal biopsies.

Dellon et al., (28) recommended in the diagnostic criteria of EoE that there should be Eosinophil-predominant inflammation on esophageal biopsy, characteristically consisting of a peak value of ≥ 15 eosinophils per high-power field (Eos / hpf). Our data are similar to data revealed by Dellon. (29) who reported that, other associated features include eosinophilic microabscesses (defined as clusters of at least 4 eosinophils), eosinophil degranulation (where eosinophil granule proteins are observed extracellularly), basal zone hypertrophy, and spongiosis or dilated intercellular spaces. Sperry et al., (30) reported that Minor features include chronic inflammatory infiltrate into the lamina propria with fibrosis of the lamina propria, hyperplasia of muscular layers and basal epithelial cells with lengthening of lamina propria papillae, and intercellular edema.

The number of biopsies taken in our study was in agreement with a report of 66 adults, the sensitivity was 100 percent after obtaining five biopsies compared with 55 percent with one biopsy (31). A second study found that the sensitivity for two, three, and six biopsies was 84, 97, and 100 percent, respectively (32). In our data high eosinophilic count was observed in both proximal and distal esophageal biopsies, this is in agreement with Gonsalves et al., (33) who said that, opposed to GERD-induced esophagitis, EoE often involves long segments of the esophagus, may be patchy / focal and typically involves the proximal esophagus equally, or more so, than the distal esophagus / GEJ region. Salek et al., (34) reported that peak counts were greater in the distal than in proximal biopsies. These findings arrowed to the importance of planning for mapping protocol for endoscopic biopsies for cases with suspecting eosinophilic esophagitis and importance of both proximal and distal esophageal biopsies with stressing on distal biopsies and at least six biopsies from each patient to be taken for accurate diagnosis of EoE.

Conclusion

Eosinophilic esophagitis is not uncommon disease and presented in 6 cases out of 200 patients having typical symptoms of GERD. All the positive EoE cases having history of allergy and most of them are asthmatic. Eosinophilic esophagitis is considered as a possible cause of refractory GERD, most of our EoE were having refractory GERD symptoms. EREFS is a good tool to characterize endoscopic findings of EoE. Both proximal and distal esophageal biopsies are important to diagnose eosinophilic esophagitis with distal biopsies are mandatory for diagnosis.

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