Prevalence of Eosinophilic Esophagitis in Patients with Upper Gastrointestinal Symptoms

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Abstract: Eosinophilic Esophagitis (EE) is a disease in which upper intestinal symptoms are associated with dense eosinophilic infiltration of the squamous esophageal epithelium or deeper esophageal tissue. Neither symptoms nor eosinophilia respond to the administration of a PPI. The pathophysiologic mechanisms are likely related to allergic inflammation, not to an underlying motility defect as in GERD. In this study we aimed to detect the prevalence of EE in adult patients with various upper GI symptoms and its possible overlap with GERD. This study included 70 adult patients who presented to the endoscopy unit of Al Azhar university hospitals in Cairo (Al Hussein and Sayed Galal) in the period from 1st of January 2015 till 30th of June 2015, complaining of various upper GI symptoms such as heartburn, dysphagia/odynophagia, food impaction, vomiting and abdominal pain. All patients were subjected to the following: 1- Detailed history taking and clinical examination. 2- Laboratory investigations **(**liver function tests, renal function tests, complete blood count, serum Ig E level, stool analysis and pregnancy test for female participants. 3-Upper GI endoscopy and three biopsies at least were taken from 2 different sites in the esophagus including the distal and either mid or proximal esophagus even if the esophagus appeared endoscopically normal to detect endoscopic findings suggestive of EE and to be preserved in 10% formalinand examined by histopathologist after staining with Haematoxylin and Eosin. **Results**: Mean age of the participants was 34 years with a standard deviation of 9.9 years. Eight patients were complaining of dysphagia; only three of them proved to be EE by histopathological examination in spite of normal endoscopic examination in two of them. **Conclusion:** 1- EE is more common in males and normal endoscopic examination of the esophagus does not exclude EE. 2-Dysphagia is the main presenting symptom of EE while heart burn is more common in GERD. 3- Eeosinophilic biopsy is the only inclusion criterion for diagnosis of eosinophilic esophagitis (>15 eosinophils /HPF). 4- Peripheral blood eosinophilia and serum total IgE are unreliable markers for predicting, diagnosis and follow up eosinophilic esophagitis.

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1. Introduction

Gastroesophageal Reflux Disease (GERD) is the most common cause of esophagitis. Other important, but less common causes are infections, medications, radiation therapy, systemic disease and trauma. Eosinophilic esophagitis (EE) has emerged as an important cause of esophagitis in both children and adults ***(Lucendo et al., 2009).***

Eosinophilic esophagitis (EE) has come to the forefront in individuals previously suspected as having severe, chronic gastroesophageal reflux disease. EE is a disease of children and adults characterized by an isolated, severe eosinophilic infiltration of the esophagus manifested by gastroesophageal reflux like symptoms, such as regurgitation, epigastric and chest pain, vomiting, heartburn, feeding difficulties, and dysphagia unresponsive to acid suppression therapy ***(Liacouras, 1998).***

EE is currently defined as a "chronic, immune / antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation" ***(Dellon et al., 2013).***

EE is clinicopathologic disorder diagnosed by clinicians taking into consideration both clinical and pathologic information without either of these parameters interpreted in isolation, and defined by the following criteria:

- Symptoms related to esophageal dysfunction.
- Eosinophil-predominant inflammation on esophageal biopsy,

characteristically consisting of a peak value of ≥ 15 eosinophils per high-power field.

- Mucosal eosinophilia is isolated to the esophagus and persists after aPPI trial.
- Secondary causes of esophageal eosinophilia excluded.
- A response to treatment (dietary elimination; topical corticosteroids) supports, but is not required for diagnosis ***(Dellon et al., 2013).***

EE may occur in isolation or in conjunction with eosinophilic gastroenteritis. Isolated EE was previously thought to be a rare condition. However in the last several years; numerous case series have been reported from North and South America, Europe, Asia, and Australia. The cause for this dramatic rise is likely a combination of an increasing incidence of EE as well as a growing awareness of the condition among gastroenterologists, allergists, and pathologists ***(Rothenberg, 2004).***

In adults the common presenting symptoms are dysphagia, food impaction, heartburn, and chest pain, while in children include vomiting, regurgitation, and abdominal pain. A male predisposition has been seen in both adult and pediatric cases. In many cases, misdiagnosis led to repeated endoscopies, esophageal dilatations, and a delay in the institution of appropriate medical therapy ***(Sgouros et al., 2006).***

The role of environmental allergens contributing to esophageal eosinophilia has also been suggested in humans. A case report of an adult with allergic rhinoconjunctivitis and asthma demonstrated an increase in symptoms as well as esophageal eosinophilia during pollen seasons. Interestingly, biopsies obtained during nonpollen months were normal, suggesting that tissue eosinophilia was triggered by pollen exposure***(Fogg et al., 2003).***

Endoscopic features in adults with EE include linear furrows (80%), mucosal rings (64%), small caliber esophagus (28%), white plaques/exudates (16%), and strictures (12%). It is important to note that the classic endoscopic features may be subtle and missed during endoscopy ***(Fox et al., 2002).***

Endoscopic ultrasound has also been used to demonstrate that eosinophilic infiltration may include deeper layers of the esophagus including mucosal and submucosal layers. This mucosal and submucosalfibrosis may lead to decreased compliance of the esophagus, thus contributing to the symptoms of dysphagia even in the absence of an identifiable stricture ***(Stevoff et al., 2001).***

Although the optimal diagnostic threshold of eosinophil density has not been determined, most centers use a value of >**15–20** eosinophils per high power field to differentiate EE from GERD, with the latter generally demonstrating <5 eosinophils per high power field ***(Sgouros et al., 2006).***

It has been demonstrated that the eosinophilic infiltration of the esophagus may not be evenly distributed. Therefore, it is suggested that biopsies should be obtained from both the proximal and distal esophagus to obtain a higher diagnostic yield and perhaps increase the specificity of the diagnosis ***(Stevoff et al., 2001).***

Peripheral eosinophilia can be seen in approximately 30% of adults and 60% of children and increased IgE level in 55% of adults and 40%– 73% of children ***(Sgouros et al., 2006).***

Treatments are effective in eliminating symptoms and reducing esophageal eosinophilia, each carries its own risks and benefits and ease of compliance. Dietary elimination is safe and offers lifelong treatment, but compliance can be difficult. Topical steroids offer an easily administered alternative but carries potential side effects of esophageal candidiasis, and this treatment should not be used for prolonged periods ***(Noel et al., 2010).***

Esophageal dilation, approached conservatively, may be used as an effective therapy in symptomatic patients with strictures that persist in spite of medical or dietary therapy ***(Dellon et al., 2013).***

Aim of the study:

The aim of the study was to determine the Prevalence of Eosinophilic Esophagitis in Patients with Upper Gastrointestinal Symptoms.

2. Patients and Methods

This study was conducted in the Tropical Medicine Department, Al-Zhan University Hospitals and included 70 patients who attended to the endoscopy unit complaining of various upper GI symptoms in the period from 1st of January 2015 till 30th of June 2015.

Inclusion criteria:

1- The study included 70 adult patients (above 18 years) who presented with upper GIT symptoms.
2- 2-Patients who suffered from allergic conditions including eczema, bronchial asthma, allergic rhinitis that developed upper GIT symptoms.

Exclusion criteria:

1- Known history of eosinophilic esophagitis.
2- Parasitic infestation.
3- Pregnant women.
4- Previous history of upper digestive tract surgery.
5- Known causes of eosinophilia such as malignancy, collagen, vascular disease, hypersensitivity reactions, vasculitis, sarcoidosis and drug reactions**.**
6- Previous upper digestive endoscopy showing osophageal varices, active peptic ulcer, esophageal diverticulum, Barrett's esophagus, moniliasis or achalasia.

Ethical Consideration:

Informed written consent was taken from the patients according toAl-Azhar University committee.

All patients were subjected to the following:

1-Detailed history taking and clinical examination with special emphasis on:

A- History of any allergic manifestations such as bronchial asthma, allergic rhinitis and drug allergy. B- History of drug intake: steroids, PPIs with emphasis on duration of its intake, H2 receptor blockers and

NSAIDs. C- History of smoking.

2- Laboratory investigations including:

Liver function tests, renal function tests, complete blood count, serum Ig E level, stoolanalysis and pregnancy test for femaleparticipants.

3- Upper GI endoscopy:

A- The presence of endoscopic findings suggestive of EE such as wrinkled, furrowed, ringed esophagus, covered with whitish exudates and granularity, absent vascular markings, linear fissuring, vertical furrowing, longitudinal tears, corrugation, fixed or transient concentric rings and proximal strictures ***(Nurko et al, 2001).*** B- At time of endoscopy the patients were assessed as having either obstructive or non-obstructive dysphagia and patients with obstructive dysphagia had been excluded from the study. C-The presence or absence of any other esophageal abnormality such as strictures, ulcers or masses or the presence of a hiatus hernia, GERD. D-Any other findings in the stomach or duodenum. E-At least three biopsies were taken from 2 different sites in the esophagus including the distal and either mid or proximal esophagus even if the esophagus appeared endoscopically normal.

4-Histopathological examination:

Biopsies were preserved in 10% formalin and were cut by the MICRO TOM apparatus and were examined by the same histopathologist after staining with Haematoxylin and Eosin. On the high power field the pathologist counted the eosinophils. The presences of More than 15 eosinophils/HPF was diagnostic for EE

5-Statistical analysis:

The results were collected, tabulated and statistically analyzed. P value less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 17 for Microsoft Windows.

3. Results

The study included 70 patients presenting with various upper GI symptoms. The mean age of all patients was 34 years and a standard deviation of 9.9 years (minimum=23, maximum age= 45 years). They were 46 males (65%) and 24 females (35%).

Endoscopic examination of the patients revealed many findings which are shown in ***Table (10).*** Only one case of GERD was found to have Barrett`s esophagitis by endoscopic examination.

Table (1): Endoscopic findings of the patients.

Endoscopic finding	N(70)	%
Normal esophagus	26	37.14
GERD	32	45.71
GERD with hiatus hernia	11	15.71
Hiatus Hernia	1	1.43
Duodenal ulcer or erosion	10	14.29
Gastric ulcer	1	1.43
Erosive gastritis	5	7.14

Table (2): Histopathological findings of esophageal biopsies

	Microscopic findings	N	%
GERD	Normal stratified squamous epithelium	18	18.57
	NERD	6	8.57
	ERD	42	60
	Barrett's Esophagus	1	1.43
	EE*	3	4.29
	Total	70	100.00

Microscopic examination of esophageal biopsies revealed three cases (4.29**%**) of EE (2 males and 1 female).
*One of the EE cases had additional histopathological findings of GERD.

Table (3): Patterns of esophageal mucosal injury and the subsequent group classification

Pattern of mucosal injury	N (70)	%
+ve endoscopic Findings (44)		
ERD	42	60
ERD+EE	1	1.43
Barrett`s	1	1.43
–ve endoscopic/ –ve histopathological findings(18)		
Normal esophagus	18	25.7
-ve endoscopic/+ve histopathological findings(8)		
NERD	6	8.57
EE	2	2.86

Our classification of the patients was based on both histopathological and endoscopic findings as shown in ***Table (12).*** Accordingly, out of the 70 patients, 49 had GERD (70%); 43 of them had ERD (87.8% of GERD patients; 61.4% of all patients) and 6 (12.2% of GERD patients; 8.57% of all patients) had endoscopically normal esophagus but with histopathological changes compatible with reflux esophagitis and were classified as non-erosive reflux disease (NERD) as they all also complained of heart-burn. Eighteen patients had normal endoscopic and histopathological esophagus (25.7%), and 3 patients had EE (4.28%), with an overlap between ERD and EE in one patient. One patient showed endoscopic findings of Barrett`s esophagitis and was confirmed by histopathological examination.

Table (4): Association of histopathological findings with presentingsymptoms

Histopathological Finding		NERD	ERD	EE	Total	Chi-square	
Symptom		n=6	n=43	n=3	52	X^2	P-value
	N	1	4	3	8		
Dysphagia						17.730	<0.001*
	%	16.67	9.3	100.00	15.3		
	N	0	0	3	3		
Food impaction						52.00	<0.001*
	%	0.00	0.00	100.00	5.8		
	N	6	14	0	20		
Heart burn						12.108	0.002*
	%	100.00	32.5	0.00	38.4		
	N	3	30	2	35		
Epigastric pain						0.936	0.6264
	%	50.00	69.7	66.67	67.3		
	N	1	3	0	4		
Vomiting						0.962	0.618
	%	16.6	6.9	0.00	7.7		

(*) denotes statistically significant occurrence of the relevant symptom within the same studied group.

Associations between histopathological findings and the presenting symptoms are shown in ***Table (4).*** The case which was proved to be Barrett`s was manifested clinically by heart burn. Dysphagia and food impaction occurred more significantly in eosinophilic esophagitis (*p- value*=<0.001*) in relation to other presenting symptoms.

Heart burn occurred more significantly in NERD (*p-value*=<0.001*) in relation to other presenting symptoms.

Table (5): Medical history according to the groups of the study

Histopathological Finding		NERD	ERD	EE	Total	Chi-square	
History		n=6	n=43	n=3	52	$x2$	P-value
	N	4	21	0	25		
Smoking						3.618	0.163
	%	66.67	48.8	0.00	48.1		
	N	3	26	3	32		
Use of PPI						2.233	0.327
	%	50.00	60.5	100.00	61.5		
	N	2	4	0	6		
Use of H2R antagonists						3.394	0.183
	%	33.3	9.3	0.00	11.5		
	N	0	4	2	6		
History of bronchial asthma	%	0.00	9.3	66.67	11.5	3.953	0.011*

There is statistically significant difference between EE and history of Bronchial asthma.

Table (6): Relation between Peripheral eosinophilia in patients with EE and other diseases (ERD, NERD)

	Peripheral eosinophilia		T-test	
	Range	Mean+SD	T	P-value
EE	285-360	323.15±16.5		
			0.229	
Others	277-357	318.5±34.84		
				0.819

There is no statistically significant difference between Peripheral

Eosinophilia in patients with EE and other diseases (ERD, NERD).

Table (7): Correlation between peripheral eosinophilia and Intraesophageal eosinophils in biopsy proven eosinophilic Esophagitis.

Case No	*Peripheral blood eosinophilia (10 -500) cmm*	*No. of Eos/HPF*
1	*490*	*15*
2	*280*	*20*
3	*370*	*23*
R	*-0.500*	
P-value	*0.667*	

There is no statistically significant difference between peripheral eosinophiliaand intraesophagealeosinophils in biopsy proven eosinophilic esophagitis.

Table (8): Relation between IgE level in patient with EE and others

	IgE level (IU/mL)			T-test
	Range	Mean+SD	T	P-value
EE	82-210	143.73± *62.867*		
			0.973	0.333
Others	75-198	114.67± *50.18*		

There is no statistically significant difference between IgE levels in Patients with EE and other (ERD, NERD).

4. Discussion

EE is a clinicopathologic disease that shows a worldwide distribution. It is distinctly more common in males, and it affects patients of all ages **(Potter et al., 2004).** Until recently there had been a preponderance of reports in the pediatric population. Although it is possible that EE occurs less often in adults, most likely it has been under diagnosed as recent clinical reports suggest. EE was the leading cause of food impaction and dysphagia in a suburban private practice **(Noel et al., 2010).** The most common presenting symptom of EE is dysphagia but other symptoms such as nausea, vomiting, heart burn, chest pain or abdominal pain can also occur **(Croese et al., 2003; Dellon et al., 2013).**

The aim of this work was to detect the prevalence of EE in adult patients presenting with various upper GI symptoms.

We found 3 cases of EE out of 70 adult patients presenting with upper GI symptoms (4.29%) as shown in **(Table 2).** The prevalence of EE varies with the population studied. For example, it has been estimated to be 0.4% - 1.1% in the general population **(Almansa et al., 2011; Ronkainen et al., 2007).**

This is in agreement with **Hunter et al., (2014)** who found 3 cases of EE out of 91 adult patients presenting with various upper gastrointestinal symptoms (3.3%). **Veerappan et al., (2009)** enrolled 400 consecutive adults who underwent routine upper endoscopy and found the prevalence of EE was 6.5%.

Kapel and his colleagues **(2008)** started a national pathology database to detect the prevalence of EE; they diagnosed 363 cases from 74162 participants; the age ranged from 1 to 98 years. **Jeremy** and his colleagues **(2005)** performed a study on 157 cases and found that 41 cases proved to have EE.

Several lines of evidence support a role for allergic inflammation in the pathogenesis of EE. The most obvious evidence for such involvement is the central role of the eosinophil which is often considered synonymous with allergic disease because of its accumulation in sputum in asthma, in nasal secretions

in allergic rhinitis and in the skin during flares of acute eczema **(Mikhak and Luster, 2009).** Among adults with EE, studies report personal or family histories of allergies ranging from 50 to 90%, including up to 60% with asthma **(Croese et al., 2003; Straumann et al., 2003; Potter et al., 2004).** Although clearly an atopic condition, the role of specific allergic triggers in EE remains unclear (**Carr and Watson, 2011).** In this study, 66.6% of the EE patients had history of bronchial asthma as shown in (**Table 5**). Also, **Potter et al., (2004)** found that 14 of 29 patients (48%) with documented EE had a history ofasthma, environmental allergy, or atopy. Compared with EE negative patients, EE positive patients were more likely to have asthma (32.0% vs. 10.8%) **(Veerappan et al., 2009)** Similarly, EE was positive in 22% of asthmatics **(Mackenzie et al., 2008)**.

The symptom profile is similar to that of severe GERD, but unlike GERD, EE is not resolved with acid reduction therapy, such as PPIs, and H2RA **(Brown-Whitehorn, 2010).**

The most characteristic symptom of EE in adults is intermittent dysphagia, often accompanied by food impaction **(Straumann et al., 2003; Dellon et al, 2013)**. In the current study, the main presenting symptom of EE patients was dysphagia and food impaction which were present in all three patients with EE (100%) (P value<0.001) as shown in (**Table 4)**. This is in agreement with **Hunter et al., (2014)** who found that the main presenting symptom of EE patients was dysphagia. Also there are two EE patients who suffer from epigastric pain (66.67%). None of EE patients complained of heart burn or vomiting. The most common indication for endoscopy in **Kapel et al., (2008)** was dysphagia (70%). The degree of eosinophilic infiltration was high throughout all ages and might be related to symptoms **(Kapel et al., 2008). Brian and Eldon, (2006)** stated that dysphagia was the primary presenting symptom of EE, then food impaction. Dysphagia was characterized by relatively long duration and resistance to usual treatment. Also, in **Veerappan et al., (2009)** food impaction was found in 32.0% of cases and dysphagia in 64.0%. The prevalence of food impaction was 33% in EE **(Noel et al., 2010).**

Two of the three positive cases of EE in our study (66%) showed normal endoscopic appearance of the esophagus as shown in (**Table 3**). In **Furuta et al., (2007),** 20% of EE patients had normal-appearing esophagus. **Machenzie et al., (2008)** found that 42% of patients with EE did not have the classic endoscopic picture of EE. **Veerappan etal., (2009)** found the presence of classic endoscopic findings of EE (rings, furrows, plaques, or strictures) to have a sensitivity of 72%**.** The difference may be due to the small number of patients found to have EE in our study.

In this study, 6 out of 20 patients with heartburn had NERD (30%) as shown in (**Table 4)**. **Winter et al., (1982)** found that 26% of patients with heartburn were found to exhibit normal esophageal mucosa during endoscopy.

The role of acid reflux in the pathogenesis of EE is a matter of debate. The coming years will also bring new enlightenment as to the relationship between GERD and EE. There is probably clinical crossover between these two diseases in some patients that will likely be explained as the esophageal microenvironment becomes better defined **(Mikhak and Luster, 2009).**

The prevalence of ERD in our patients was 61.4% and epigastric pain was the presenting symptom in 69.7% of them as shown in (**Table4)**. **Richter, (1992)** estimated that 25-40% of healthy adults experience symptomatic GERD, most commonly manifested clinically by epigastric pain, at least once a month. Furthermore, approximately 7-10% of the adult population experiences such symptoms on a daily basis **(Richter, 1992)**.

In this study, 11 out of 43 patients with GERD had hiatus hernia (25.6%) as shown in (**Table 1)**. **Buttar and Falk, (2001)** stated that hiatus hernia may contribute to reflux via a variety of mechanisms. Hiatus hernias can be encountered frequently in patients with GERD; however, it has been well proven that not all patients with hiatus hernias have symptomatic reflux.

In this study, the incidence of ERD in cases of EE was 33.3% as shown in (**Table 3)**. Which is in agreement with **Kapel et al., 2008)** who stated that the incidence of GERD in EE was 27.1%.

To distinguish between GERD and EE, patients with EE are more likely to be male and tend to have more dysphagia, asthma, and other atopic diseases; patients with GERD tend to have more heart burn, but no single symptom or associated condition distinguishes EE from GERD **(Furuta et al., 2007)**. In this study, while dysphagia was the primary symptom in EE, epigastric pain and heart burn were more common in patients with GERD as shown in (**Table 4)**. In **Jeremy et al., (2005)**, who included 157 cases with esophagitis, EE was more in males; dysphagia was present in 63% while heart burn and epigastric pain were more in non EE.

Endoscopic findings of EE include esophageal rings, strictures, narrow-caliber esophagus, linear furrows, white plaques or exudates, and pallor or decreased vasculature **(Dellon et al., 2009; Sgouros et al., 2006).** In **Jeremy et al., (2005),** endoscopic esophageal ring was more in EE while hiatus hernia was more in non EE. Two of the 3 positive cases of EE in this study (66%) showed normal endoscopic appearance of the esophagus and the third had an

overlap with ERD as shown in (**Table 3**). However, the small number of patients found to have EE in our study may have precluded us from stating a specific endoscopic finding for this disease. Besides, the endoscopic features of EE may be subtle and overlooked at endoscopy **(Moy et al., 2011; Croese et al., 2003)**. One adult series of histologically confirmed EE reported 8.8% of patients without any apparent endoscopic features (**Sgouros et al., 2006)**. In a meta-analysis, the endoscopic examination was normal in 17% of cases **(Kim et al., 2012).** However, esophageal mucosal furrows were present in 30 of 31 EE patients (97%) **(Croese et al., 2003)** and the presence of classic findings of EE on endoscopy (rings, furrows, plaques, or strictures) was the strongest predictor of this disease process with a sensitivity of 72%, specificity of 89%, and negative predictive value of 98% **(Veerappan et al., 2009).** On the other hand**, (Machenzie et al., 2008)** found that 13/31 (42%) of EE patients did not have the classic endoscopic findings (rings +/− furrows) and would have been missed without esophageal biopsies. Consequently, although a high degree of suspicion for EE must be maintained for patients that have endoscopic features of this disease, the presence or absence of endoscopic findings is insufficient to make a diagnosis. Esophageal biopsies should be obtained from all patients who present with symptoms of EE, regardless of the endoscopic appearance of the esophagus **(Kim et al., 2012)**. Also, it is advised that esophageal biopsies routinely be taken in the clinical setting of unexplaineddysphagia, refractory heartburn, or chest pain regardless of endoscopic findings as endoscopic mucosal biopsy remains the most important diagnostic test for EE and the diagnosis of EE is ultimately established histologically **(Furuta et al., 2007).** Esophageal biopsies demonstrate often marked epithelial basal hyperplasia and extensive infiltration of the epithelium by eosinophils. The changes occur not just in the distal esophagus, as in GERD, but also in the mid and upper esophageal mucosa, a feature that is often useful in the differentiation of EE from reflux esophagitis. Eosinophils generally number in excess of 20 to 24/HPF (Rothenberg et al., 2004**; Orenstein et al., 2000)**. There are limited data to support routine gastric or duodenal biopsies in adults in the absence of symptoms or endoscopic abnormalities suggesting other gastrointestinal disorders, although it is reasonable for these biopsies to be performed **(Liacouras et al., 2011)**. The finding of erosive esophagitis and heart burn is not specific for GERD and does not exclude EE **(Furuta et al., 2007).**

Molina et al., (2008), reported two cases in which refluxesophagitis and EE overlap, which were similar in terms of symptoms, endoscopic reflux lesions, motor esophageal alterations, high-density eosinophilia in upper-mid esophagus biopsies and good clinical response to PPIs, but with different endoscopic and histopathological outcomes after PPI therapy. They stated that the interaction between these diseases may be more complex than originally thought and may depend more on individual patient characteristics. They suggested that an initial trial of PPI therapy in patients with clinical, endoscopic and pathologic findings of EE is warranted. Lack of a response to PPI may reinforce a diagnosis of EE, but a clinical response to PPI may not rule out quiescent EE. Also esophageal pH measurements and histopathological data of patients on PPI treatment are important in cases with overlapping GERD and EE in order to evaluate the role of each disease **(Molina et al., 2008).**

In this study, only (6) 12.2% of histopathologically GERD patients (49) had NERD diagnosed on the basis of the presence of heartburn and histopathological changes compatible with reflux esophagitis in a normal endoscopic esophagus as shown in (**Table 3)**. The changes were detected in mid-esophageal biopsies. There has been little standardization of biopsy techniques or tissue processing in ERD and NERD patients. Biopsies have been obtained at the squamocolumnar junction, or at 1, 2, 3 and 5 cm above it. Furthermore, there is no consensus on the number of biopsy specimens obtained, or the location around the inner circumference of the esophagus at which biopsies should be taken. This issue is especially important since the severity of exposure to refluxate decreases with increasing distance from squamocolumnar junction and the distribution of mucosal injury may be patchy **(Modlin et al., 2009).** However, in the attempt to better understand the mechanisms involved in the perception of gastroesophageal reflux, some observations have pointed out the role of the acid extent into the middle-proximal esophagus **(Bredenoord et al., 2006).** Indeed, in NERD patients, independently of the acid exposure time, reflux episodes reaching the proximal esophagus were perceived more than those confined to the distal esophagus **(Cicala et al., 2003).** In this study there is no significant statistical difference between both EE patients and other oesophageal disorders as regard peripheral blood eosinophilia as shown in (**Tables 6, 7)**. So, the peripheral blood eosinophilia is not a cardinal predictor or diagnostic element in eosinophilic esophagitis. This study agrees with **Konnikoff et al., (2006)** as Peripheral eosinophilia is not a reliable sign for EE as it is not always present. When identified, it is difficult to differentiate whether peripheral eosinophilia occurs as a marker for EE or

other comorbid diseases. In this study there is no significant statistical difference between both EE patients and other oesophageal disorders as regard serum IgE (**Table 8)**. Similar to patients with allergic rhinitis, EE patients have total IgE usually within the normal range. On the other hand, the delayed response to allergen exposure and suspected barrier defect are more consistent with atopic dermatitis and asthma **(Vicario et al., 2010).**

Conclusion

1-EE is more common in males.
2-Normal endoscopic esophagus does not exclude EE.
3-Dysphagia is the main presenting symptom of EE while heart burn is more common in GERD.
4-biopsy is the only inclusion criterion for diagnosis of eosinophilic esophagitis (>15 eosinophils /HPF).
5-Peripheral blood eosinophilia and serum total IgE are unreliable markers for predicting, diagnosis and follow up eosinophilic esophagitis.

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