Study on the association between eosinophilic esophagitis and bronchial asthma in Egyptian patients with esophageal symptoms
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Introduction
Eosinophilic esophagitis (EoE) is a chronic inflammatory disease of the esophagus in which eosinophils play a major role in its pathogenesis and is presented clinically by esophageal dysfunction. EoE represents the second most common cause of chronic esophageal disease after gastroesophageal reflux disease (GERD) and is considered the most common cause of dysphagia in both adults and children. Asthma is a well-known chronic inflammatory disorder of the airways that involves several inflammatory cells including eosinophils. Multiple inflammatory mediators developed the characteristic pathophysiological changes that resulted in airway obstruction and appearance of symptoms of cough and breathlessness. This study aimed to study the incidence of EoE in Egyptian patients with bronchial asthma and address the patient’s characters and risk factors that increases the association.

Settings and design
This study was carried out on Egyptian asthmatic patients with esophageal symptoms. From 200 asthmatic patients, only 89 patients had esophageal symptoms (heartburn, regurgitation, or dysphagia) and were prepared for endoscopy.

Patients and methods
Upper gastrointestinal tract endoscopy was performed on all 89 cases and the findings were reported. Esophageal biopsy was taken from all cases and examined histopathologically for EoE criteria.

Results
The results showed that about 11% of asthmatic patients who suffered from GERD symptoms had associated EoE confirmed by esophageal biopsy and histologic findings. The incidence of EoE was increased in atopic asthmatic patients who had high immunoglobulin E.

Conclusion
Asthmatic patients who suffered from GERD symptoms should be assessed for EoE by endoscopic and histopathological examination.

Keywords:
asthma, eosinophilic esophagitis, eosinophils

Background
Eosinophils are a subtype of leukocytes with multifunctions. It is implicated in the pathogenesis of many inflammatory diseases in all body systems [1]. Normally, eosinophils are distributed throughout the gastrointestinal tract (GIT) except in the esophagus [2]. Once eosinophils are present in the esophagus, an associated pathological process is present. Eosinophilic esophagitis (EoE) is a chronic inflammatory disease of the esophagus in which eosinophils play a major role in its pathogenesis and presented clinically by esophageal dysfunction [3,4]. EoE represents the second most common cause of chronic esophageal disease after gastroesophageal reflux disease (GERD) [5] and is considered the most common cause of dysphagia in both adults and children [6]. Previously, EoE was known to be a form of food allergy caused by a TH2-cell-mediated immune reaction [7], which might be prevented by avoiding exposure to certain food protein antigens in the diet [8]. The 2011 Consensus Guidelines defined EoE as a chronic, immune/antigen-mediated disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation [4]. It was reported that EoE is the worst allergic disease between all chronic allergic conditions [9].

Many previous studies have shown information on the prevalence of different atopic conditions in pediatric [10,11] and adult [12,13] patients diagnosed as EoE in comparison with control group. From these
information, we can say that there is a higher frequency of asthma, rhinoconjunctivitis, eczema, and food allergies in patients with EoE than control groups [14,15]. The underlying cause of EoE was studied by different researchers and they conclude the causes to be either immune or antigenic response which is associated with endoscopic, histologic, and genetic abnormalities [16–20].

Theoretically and practically EoE was included in the differential diagnosis of various clinical presentations by multiple subspecialties (adult and pediatric gastroenterology, allergy/immunology, pulmonary medicine, and otolaryngology) [4]. The diagnosis of EoE depends on the clinicopathologic features of the disease. Symptoms related to esophageal dysfunction are the clinically important symptoms for diagnosis of EoE. Pathologically, the biopsy specimens must show eosinophil-predominant inflammation with at least 15 eosinophils/high-power field (HPF) (peak value), which is considered a minimum threshold for the diagnosis of EoE [4]. In previous studies, the sex distribution was at a male/female ratio of, 3 : 1. The predominant age of presentation was in the childhood or during the third or fourth decades of life; however, EoE can occur at any age [13,21].

Asthma is a well-known chronic inflammatory disorder of the airways that involves several inflammatory cells including eosinophils. Multiple inflammatory mediators developed the characteristic pathophysiological changes that resulted in airway obstruction and appearance of symptoms of cough and breathlessness [22]. It was found in the previous studies that eosinophils are present in increased numbers in the airways of asthmatic patients and the released basic proteins may damage airways epithelial cells, causing airway remodeling [23,24]. It is reported that two-thirds of patients with mild-to-moderate asthma have increased sputum eosinophils [25]. Eosinophils can cause a heterogeneous group of disorders involving many major organ systems including the respiratory system and GIT as well. EoE and asthma are frequently associated and have a number of similarities in their pathogenesis.

This work aimed to study the incidence of EoE in Egyptian patients with bronchial asthma and address the patient’s characteristics and risk factors that increase the association.

Patient and methods

Patients
This study was conducted in Benha University Hospital Chest Department in cooperation with internal medicine and histopathology departments – Al-Azhar University Hospitals. The study was done during the periods between July 2017 and September 2018.

Two hundred asthmatic patients were recruited from the pulmonary outpatient clinic. Those patients were evaluated for esophageal symptoms using the frequency scale for the symptoms of GERD [26]. All patients underwent through history taking, full clinical examination, plain chest radiographs, complete stool and urine analysis, total immunoglobulin E (IgE), complete blood count with differential count, spirometry, and abdominal ultrasonography. The exclusion criteria were patients under treatment with systemic corticosteroid, patients with parasitic infestation in stool analysis, pregnant or nursing women, previous history of upper digestive tract surgery, decompensated chronic diseases, previous upper digestive endoscopy showing active peptic ulcer, esophageal diverticulum, Barrett’s esophagus or esophageal obstruction, known causes of eosinophilia such as malignancy, collagen vascular disease, hypersensitivity reactions, vasculitis (including charge Strauss syndrome), sarcoidosis, hypoadrenalism, and drug reactions. From the 200 asthmatic patients only 89 patients met the inclusion criteria for upper GIT endoscopic assessment. Histopathological examinations for the endoscopic biopsies were done to all of them.

The study was divided into two groups: group 1 included asthmatic patients without esophageal symptoms (111) and group 2 included asthmatic patients with esophageal symptoms (89). All the results were tabulated and statistically analyzed using SPSS, version 24 (SPSS Inc., Chicago, Illinois, USA). P values of less than 0.05 were considered significant [27].

Methods
An informed written consent was signed by each patient after explaining the purpose and the methods of the study. The study was approved by the local ethics committee. The patients who refused to share in the study were excluded from the study.

Spirometry
The patient data (sex, age in years, height in centimeters, weight in kilograms, BMI) were entered to a machine before doing the test. All results were calculated as percent of predicted (% predicted) except for forced expiratory volume in the first second (FEV1)/forced vital capacity. Spirometry was done
using SensorMedics Vmax series, 2130 spirometer, V 6200 Autobox, 6200 DL. Flow/volume loop was performed to all cases. Patients who obtained FEV1 was less than 80% of predicted and an FEV1/forced vital capacity less than or equal to 0.7 proceed to do a bronchodilator test. The test was repeated 20 min after the patient received two puffs of Salbutamol (200 μg) via a metered dose inhaler. The diagnosis of asthma was confirmed if there is a positive reversibility test. This was obtained if the postbronchodilator FEV1 was improved more than 12% and more than 200 ml from baseline and lung volumes returned to the predicted normal range [28].

Upper gastrointestinal tract endoscopy
The selected asthmatic patients (89 out of 200 patients) who had one or more of the esophageal symptoms such as reflux (heartburn or regurgitation) or symptoms of esophageal complications (dysphagia or history food impaction) [29] underwent clinical assessment (medical history and examination). The selected patient with positive symptoms received empirical proton pump inhibitors for 8 weeks prior to the endoscopy to exclude proton pump inhibitors responsive EoE [30]. All patients were subjected to upper GIT endoscopy under conscious sedition (by Midazolam 5–8 mg intravenously) after written consent for the sedation and the procedure for endoscopic assessment mainly for esophagus and esophageal mucosa as well as for stomach and duodenum with biopsies [31]. Endoscopic assessment of esophageal mucosa and cardia was done for presence of the GERD by presence of mucosal damage as the lower segment erosive esophagitis, esophageal ulcers, benign stenosis, incompetent cardia, presence of sliding hiatal hernia with or without gastric contents refluxate. Endoscopic picture of the EoE such as longitudinal furrows, esophageal circular rings (trachization), or whitish plaque were also evaluated [32]. All patients were subjected to multiple esophageal mucosal biopsies (at least four esophageal mucosal biopsies were taken for each patient) for histopathological examination [33].

Pathological examination
This study involved 89 cases of esophageal biopsies. The specimens were received, processed, and embedded according to the policy and procedures of examinations of small biopsies [34]. The biopsies received were at least four biopsy specimens from two separate sites in the esophagus mainly proximal and middle with occasional lower esophageal part biopsy. From each paraffin-embedded block, two sections (3–4 μm each) were prepared for routine hematoxylin and eosin stain. All histological staining was performed in accordance with conventional procedures [35]. Sections stained by hematoxylin and eosin were examined to detect the number of eosinophils in the esophageal mucosa, abscess formation, associated dysplasia, or reflux esophagitis; all cases having less than 15 eosinophils/HPF were excluded.

Diagnostic criteria of eosinophilic esophagitis
The presence of intraepithelial eosinophils at least 15/HPF in any one field is considered diagnostic for EoE (eos/HPF), while the presence of 6–14/HPF is considered indeterminate; eosinophils may be diffuse or in clusters and may form microabscess which is defined as a cluster of four or more eosinophils and is mainly located in superficial layers of the mucosa. The eosinophils should present only in the esophagus and the presence of eosinophils in other parts of the intestine suggest eosinophilic gastroenteritis [36]. Other less specific histological features that have occurred with EoE include intercellular edema (spongiosis), eosinophilic degranulation, marked basal cell hyperplasia, and fibrosis of the lamina propria if the biopsy contains subepithelial layers. Histopathologic features without clinical correlation cannot diagnose EoE [37].

Statistical analysis
Patients’ characteristics and data were presented as mean±SD unless otherwise stated. Comparisons were performed by unpaired t tests for quantitative data. A P value of less than 0.05 was used to indicate differences between the groups that were statistically significant. Data analysis was performed with a commercially available statistical analysis software package (SPSS 20.0 for Windows; SPSS Inc.).

Results
This study included 200 patients diagnosed with asthma. The mean age was 40.2±13.3. The study included 120 men and 80 women. Patients were reviewed for GERD symptoms and 89 cases documented one or more positive GERD symptoms. Accordingly, the patients were divided into two groups: group 1 (111) included asthmatic patients without GERD symptoms and group 2 (89) asthmatic patients with GERD symptoms. Table 1 shows the demographic, spirometry, and laboratory results of both groups. Data showed that the mean age of group 2 is higher than group 1 with nonsignificant statistical differences between both groups. As regards spirometry results it was found to be better in group 1
than group 2 with nonsignificant statistical differences between both groups. For allergic parameters (IgE and blood eosinophils) they were higher in group 2 than group 1 with highly significant statistical differences between both groups. Liver enzymes and bilirubin showed higher figures in group 1 than group 2 with nonsignificant statistical differences between both groups. All results were within normal levels.

Table 2 shows the number and percentage of different symptoms and signs for all patients. As shown, heartburn documents the higher presentations (84%) followed by regurgitation (58%) and a combination of both symptoms in 42% of patients in group 2. Dysphagia was present in 20% of patients.

The endoscopic findings are illustrated in Table 3 which shows normal esophageal picture in nine cases, erosive esophagitis different grades in 80 cases, esophageal stenosis in one case, esophageal rings in 10 cases, longitudinal furrows in nine cases, and white plaques in seven cases. Other endoscopic findings showed 11 cases with hiatal hernia, 33 cases with antral gastritis, two cases with pangastritis, one case with gastric ulcer, and three cases with biliary reflux. For the duodenum, duodenitis was found in seven cases without any duodenal ulcers. Positive campylobacter-like organism (CLO) test was found in 11 cases for H. pylori screening (Table 3 and Fig. 1).

The histopathological diagnosis is shown in Table 4 which shows normal esophageal picture in nine cases, erosive esophagitis different grades in 80 cases, esophageal stenosis in one case, esophageal rings in 10 cases, longitudinal furrows in nine cases, and white plaques in seven cases. Other endoscopic findings showed 11 cases with hiatal hernia, 33 cases with antral gastritis, two cases with pangastritis, one case with gastric ulcer, and three cases with biliary reflux. For the duodenum, duodenitis was found in seven cases without any duodenal ulcers. Positive campylobacter-like organism (CLO) test was found in 11 cases for H. pylori screening (Table 3 and Fig. 1).
histological diagnosis which included mild reflux esophagitis in 20 cases, moderate reflux esophagitis in 35 cases, and severe reflux esophagitis in 24 cases. Features of EoE cases includes eosinophils of more than 15/HPF which was found in 10 samples, microabscesses and chronic slough in eight samples, spongiosis (dilated intracellular spaces) in nine samples, and basal cell hyperplasia in nine samples. (Table 4). The full histopathologic features of all cases with EoE are shown in Table 5. The full four histopathologic features of EoE were found in six cases while the other four cases had some of them.
This study was carried out on Egyptian asthmatic patients with esophageal symptoms. The study included 200 asthmatic patients. From those patients only 89 patients had esophageal symptoms (heartburn, regurgitation, or dysphagia). Upper GIT endoscopy was done to all 89 cases and the findings were reported. Esophageal biopsy was taken from all cases and examined histopathologically for EoE.

### Table 5 Detailed histopathologic features for each

<table>
<thead>
<tr>
<th>Case features</th>
<th>Eosinophils of more than 15/HPF</th>
<th>Eosinophilic microabscesses</th>
<th>Spongiosis</th>
<th>Basal cell hyperplasia</th>
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<tbody>
<tr>
<td>Case 1</td>
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<td>+</td>
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<td>+</td>
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<tr>
<td>Case 2</td>
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<td>+</td>
<td>+</td>
<td>Nil</td>
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<tr>
<td>Case 3</td>
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<td>+</td>
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<tr>
<td>Case 5</td>
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<tr>
<td>Case 6</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Case 7</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>Case 8</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Case 9</td>
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<td>Case 10</td>
<td>+</td>
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HPF, high-power field.

### Discussion

This study was carried out on Egyptian asthmatic patients with esophageal symptoms. The study included 200 asthmatic patients. From those patients only 89 patients had esophageal symptoms (heartburn, regurgitation, or dysphagia). Upper GIT endoscopy was done to all 89 cases and the findings were reported. Esophageal biopsy was taken from all cases and examined histopathologically for EoE.

Histopathological finding. Slide of mucosal biopsy of the esophagus showing marked eosinophilic infiltrate with eosinophilic slough of superficial epithelial cells and microabscesses which are defined as clusters of at least four eosinophils and a superficial layering as seen in images (a), (c), (d), and (e) (red arrows); basal cell hyperplasia as seen in image (f) (blue arrow); and dilated intracellular spaces (spongiosis) as seen in image (b) (yellow arrow).
criteria. The study was divided into two groups: Group 1 included asthmatic patients without esophageal symptoms (111 cases) and group 2 included asthmatic patients with esophageal symptoms (89 cases).

EoE is an immune-mediated, chronic eosinophilic inflammatory disease and is characterized by symptoms of esophageal dysfunction [3,4]. The associated other atopic diseases with EoE were studied previously in both children and adults [10–13]. EoE is strongly associated with allergy either airborne or food allergy [38]. In the current study, asthma as a main atopic respiratory disease was chosen and studied to assess the frequency and incidence of EoE in asthmatic patients. The results showed that about 11% of asthmatic patients who suffered from GERD symptoms had associated EoE confirmed by esophageal biopsy and histologic findings. The incidence of EoE increased in atopic asthmatic patients who had high IgE and this observation was matched with that of Mulder et al. [39]. Bronchial asthma is usually associated with esophageal symptoms specially GERD and is considered one of the extrasophageal syndromes of GERD [40]. The current results showed an increased prevalence of EoE in men than women (60% men versus 40% women with an average age of 40.2±13.3) which is in agreement with Veerappan et al. [41] who reported that EoE is more prevalent in men than women younger than 50 years. In the current study, the most common presenting symptoms of EoE are heartburn, regurgitation, and dysphagia presenting more than 50% of cases (75, 52, 18%, respectively). These results were similar to previous studies which reported that dysphagia was present in 64.0 [41] and 89% of EoE patients [42].

In the current study, four esophageal mucosal biopsies were taken from each case and this was matched with Nielsen et al. [43] who document that the recommended least number of biopsies to establish the morphologic diagnosis of EoE are four biopsies and more. EoE was confirmed by the presence of eosinophilic infiltration of the endothelium by eosinophils of more than 15/HPF [32]. The association between asthma and EoE may be related to atopy. In the previous study, the association between EoE and other atopic diseases such as asthma, eczema, or allergic rhinitis was found in 50–80% of patients with EoE [44]. Aeroallergens were considered as a trigger for EoE exacerbation and support the theory which considered atopy to play a role in the pathogenesis of EoE [45].

Conclusion
Asthmatic patients who suffered from GERD symptoms should be assessed for EoE by endoscopic and histopathological examination especially if they had associated high IgE or increased blood eosinophils.

Limitations
Lack of control group and a small sample size.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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