Eosinophilic Esophagitis and Gastroesophageal Reflux Disease: Overlapping Conditions and Diagnostic Challenges

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Article

Eosinophilic Esophagitis and Gastroesophageal Reflux Disease: Overlapping Conditions and Diagnostic Challenges

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Abstract

Background: Eosinophilic esophagitis (EoE) and gastroesophageal reflux disease (GERD) are distinct conditions, yet they often exhibit overlapping clinical, endoscopic, and histological features. Aim: This study aims to assess the prevalence of GERD among patients with EoE and to identify risk factors for both typical and atypical GERD symptoms. Methods: We conducted a population-based retrospective analysis of patients diagnosed with EoE and collected data on demographics, GERD diagnosis, symptoms, comorbidities, and laboratory results. GERD symptoms were classified as typical (e.g., heartburn and regurgitaion) or atypical (e.g., hoarseness and cough). Results: Of the 2,496 patients with EoE (73.2% male), 48.5% exhibited GERD symptoms—26.2% prior to and 30.5% following the diagnosis of EoE. Typical symptoms predominated before EoE diagnosis (26% vs. 4.3% after diagnosis), whereas atypical symptoms were more frequent after diagnosis (28% vs. 0.4% before diagnosis), with cough increasing from 0.4% to 27.4%. In the multivariate analysis, allergic rhinitis (odds ratio [OR 1.40, 95% confidence interval [CI]; 1.15–1.75, $p < 0.001$) and hiatal hernia (OR 2.47, 95% CI 1.75–3.47, $p < 0.001$) predicted typical GERD symptoms, whereas asthma (OR 1.50, 95% CI 1.28–1.85), food allergy (OR 1.36, 95% CI 1.08–1.70), and elevated eosinophil counts (OR 2.00, 95% CI 1.44–2.73) were associated with atypical GERD symptoms. Conclusion: Approximately half of patients with EoE are present with GERD symptoms, with a tendency toward more atypical symptoms after EoE diagnosis. Identifying key predictors and risk factors may improve diagnostic accuracy and facilitate the development of targeted treatment strategies.

Keywords: Eosinophilic esophagitis; Gastroesophageal reflux disease; typical symptoms

Introduction

Eosinophilic esophagitis (EoE) and gastroesophageal reflux disease (GERD) are distinct gastrointestinal disorders that frequently present with overlapping clinical features that complicate their diagnosis and management. A previous study involving 100 patients with GERD found that 6% were also diagnosed with EoE, with 9.7% exhibiting refractory symptoms despite proton pump inhibitor (PPI) treatment [1]. GERD is common in the general population, with an estimated

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incidence of 9,838 cases per 100,000 individuals and a marked increase in prevalence over recent decades [2]. Conversely, EoE, traditionally classified as a rare disorder, has demonstrated increasing incidence and prevalence, thereby attracting substantial clinical and research interest [3]. EoE is characterized by an immune-mediated response that leads to the accumulation of eosinophils within the esophageal epithelium, resulting in inflammation and a range of symptoms, including dysphagia (difficulty swallowing) and food impaction [4,5]. Despite its previously perceived rarity, the frequency of this condition has increased, necessitating enhanced awareness among healthcare providers. In contrast, GERD is defined as the retrograde flow of gastric contents into the esophagus, causing symptoms such as heartburn and regurgitation. It is recognized as one of the most common gastrointestinal disorders worldwide and can lead to serious complications, including esophagitis, esophageal strictures, and Barrett's esophagus. The overlapping symptoms of EoE and GERD present significant diagnostic challenges [6]. A thorough understanding of the interrelationship between these conditions is required. Discerning between the two is crucial for developing effective treatment strategies, as therapies suitable for GERD may not be effective for EoE. This study aimed to investigate the prevalence of GERD among patients diagnosed with EoE, focusing on both typical and atypical GERD symptoms, and to identify predictors of GERD in this unique patient population.

Methods

Study Design and Population

This retrospective, population-based analysis included patients with a recorded diagnosis of eosinophilic esophagitis (EoE) identified using ICD-9/10 codes from the Clalit Health Services (CHS) database between 2000 and 2024. The CHS database utilizes the MdClone platform and maintains comprehensive longitudinal electronic health records for over 5 million insured individuals, representing more than half of Israel's population. This database includes detailed demographic, diagnostic, laboratory, and medication prescription data collected from hospitals and community healthcare settings. Patients with gastroesophageal reflux disease (GERD) were similarly identified using ICD-9/10 coding and corresponding medical records, with particular attention to the timing of EoE diagnoses. GERD diagnosis included any related diagnosis, including heartburn, regurgitation, esophageal reflux, and esophagitis. EoE diagnoses were identified according to the appearance of EoE as one of the chronic diagnoses in the community or hospital setting.

Data Collection

We collected demographic data, including age at diagnosis, sex, ethnicity, and socioeconomic status, from patients diagnosed with EoE. Information regarding the diagnosis of GERD, as well as typical and atypical GERD symptoms and comorbidities, was also gathered. The diagnoses of GERD, heartburn, and regurgitation were classified as typical GERD symptoms, whereas hoarseness and cough were considered atypical GERD symptoms. Chest pain, a symptom that may manifest in both conditions, was documented separately, excluding individuals with ischemic heart disease (IHD). Additionally, the initiation of medications, such as proton pump inhibitors (PPIs), budesonide (Jorveza), and dupilumab, were recorded. Laboratory data within six months of EoE diagnosis were retrieved, including hemoglobin levels, white blood cell (WBC) count, platelet count (PLT), and eosinophil count (both absolute number and percentage).

Statistical Analysis

Categorical variables were summarized as frequencies and percentages, and comparisons were made using Chi-square test or Fisher's exact tests. Continuous variables are expressed as means ± standard deviations and were compared using Student's t-test, with statistical significance set at $p < 0.05$. A multivariate logistic regression model was employed to determine the independent predictors of GERD among patients with EoE, and this model included covariates such as age.

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This study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Institutional Helsinki Committee (approval number: 0057-25-SOR). The requirement for informed consent was waived due to the retrospective design of the study and the anonymity of the patients.

Results

In this study, we included 2,496 patients diagnosed with eosinophilic esophagitis (EoE), of whom 1,828 (73.2%) were male. The prevalence of gastroesophageal reflux disease (GERD) symptoms before and after EoE diagnosis is summarized in Table 1. Among patients with EoE, 48.5% reported experiencing typical or atypical GERD symptoms. Specifically, 31.3% reported GERD symptoms after the diagnosis of EoE, while 26.2% experienced these symptoms beforehand.

Table 1. Typical and Atypical Symptoms of GERD in Patients before and after EoE diagnosis.

	n=2496	**n=2496**	
GERD symptoms	Before EoE diagnosis	After EoE diagnosis	Total
Heartburn	135 (5.4)	43 (1.7)	178 (7.1)
GERD	543 (21.8)	63 (2.5)	606 (24.3)
Hoarseness	1 (0)	57 (2.3)	58 (2.3)
Regurgitation	48 (1.9)	5 (0.2)	53 (2.1)
Cough	10 (0.4)	683 (27.4)	693 (27.8)
Chest pain	385 (15.4)	149 (6)	534 (21.4)
Laryngitis	253 (10.1)	41 (1.6)	294 (11.7)
Reflux Esophagitis	801 (32.1)	222 (8.9)	1023 (41)
Hiatal hernia	173 (6.9)	54 (2.2)	227 (9.1)
Typical symptoms (heartburn, regurgitation, GERD)	650 (26)	107 (4.3)	739 (29.6)
Atypical symptoms Hoarseness, cough	11 (0.4)	710 (28.4)	721 (28.9)
Typical and atypical symptoms	654 (26.2)	782 (31.3)	1211 (48.5)
Any PPI	707 (28.3)	1174 (47)	1881 (75.4)
Budesonide	0	242 (9.7)	242 (9.7)
Dupilumab	3 (0.1)	64 (2.6)	67 (2.7)

Typical GERD symptoms, including GERD diagnoses, regurgitation, and heartburn, were observed in 26% of patients prior to EoE diagnosis but declined to 4.3% following diagnosis. In contrast, atypical symptoms such as hoarseness and cough were notably more frequent after the diagnosis of EoE, reported by 28.9% of patients compared with only 0.4% before diagnosis. Chest pain, which may be associated with both conditions, was present in 15.4% of patients before and 6% after EoE diagnosis.

Diagnoses of laryngitis, reflux esophagitis, and hiatal hernia were more prevalent prior to EoE diagnosis, with respective frequencies shown in Table 2: 10.1% vs. 1.6% (laryngitis), 32.1% vs. 8.9% (reflux esophagitis), and 6.9% vs. 2.2% (hiatal hernia). Cough was particularly prevalent after EoE diagnosis, occurring in 27.4% of patients compared with only 0.4% in the control group.

Table 2. Atopic comorbidities among the EoE patients.

	n=2496	**n=2496**	
	Before EoE diagnosis	After EoE diagnosis	Total
Asthma	1007 (40.3)	179 (7.2)	1186 (47.5)

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Rhinosinusitis / allergic rhinitis	623 (25)	206 (8.3)	829 (33.2)
Nasal polyps	42 (1.7)	10 (0.4)	52 (2.1)
Atopic dermatitis	580 (23.2)	228 (9.1)	808 (32.4)
Food allergy	472 (18.9)	134 (5.4)	606 (24.3)
Food impaction/ foreign body	254 (10.2)	52 (2)	306 (12.3)
Esophageal stenosis	70 (2.8)	48 (1.9)	118 (4.7)
Barrett's Esophagus	8 (0.3)	16 (0.6)	24 (1)

data presented as n (%).

Throughout the study, as detailed in Table 3, 75.4% of the patients were treated with proton pump inhibitors (PPIs). Of these, 47% initiated PPI treatment following their EoE diagnosis, while 28.3% began treatment prior to diagnosis. Additionally, 9.7% of patients received budesonide and 2.6% were treated with dupilumab.

Table 3. Univariate and cox regression predictors for typical and atypical GERD symptoms.

Logistic regression typical GERD symptoms after EoE	**Univariate analysis**			**Multi-variate analysis**		
	OR	95% CI	p-value	OR	95% CI	p-value
Age at EoE diagnosis	1.018	1.013-1.022	<0.001	1.011	1.006-1.016	<0.001
Smoking	1.696	1.152-2.498	0.007	0.952	0.665-1.542	0.952
Allergic rhinitis/ sinusitis	1.606	1.318-1.958	<0.001	1.424	1.157-1.752	<0.001
Nasal polyps	2.387	1.291-4.411	0.006	1.486	0.779-2.835	0.229
Eosinophilia ≥6%	0.833	0.681-1.018	0.074	0.931	0.756-1.146	0.500
Hiatal hernia	3.414	2.496-4.669	<0.001	2.472	1.759-3.476	<0.001
Cox regression for atypical GERD symptoms after EoE	Univariate analysis			Multi variate analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Age at EoE diagnosis	0.987	0.982-0.992	<0.001	0.995	0.989-1.000	0.070
Smoking	0.537	0.332-0.867	0.011	0.726	0.437-1.206	0.216
Asthma	1.767	1.482-2.107	<0.001	1.542	1.281-1.855	<0.001
Atopic dermatitis	1.512	1.240-1.844	<0.001	1.188	0.963-1.464	0.107
Food allergy	1.778	1.441-2.194	<0.001	1.363	1.087-1.709	0.007
Eosinophilia ≥6%	1.367	1.134-1.648	0.001	0.679	0.500-0.924	0.014
Eosinophiles ≥500	1.753	1.457-2.110	<0.001	2.019	1.448-2.738	<0.001

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Discussion

This study demonstrated a high prevalence and overlap of gastroesophageal reflux disease (GERD) among patients with eosinophilic esophagitis (EoE). Typical GERD symptoms were more common before EoE diagnosis, whereas atypical symptoms increased thereafter. These findings suggest that reflux evaluation should prioritize anatomical causes and that concurrent management of EoE and atopy should be considered for patients presenting with atypical GERD symptoms.

EoE and GERD share overlapping symptoms that can lead to diagnostic confusion. In our study, approximately half of the patients with EoE reported GERD symptoms; some experienced these symptoms before their EoE diagnosis, while others developed these afterward. Notably, a substantial proportion of patients exhibited atypical symptoms following their EoE diagnosis. Previous research has shown that approximately 10% of patients with PPI-refractory GERD are ultimately diagnosed with EoE[1]. Another study of pediatric patients with macroscopic esophagitis on upper gastrointestinal endoscopy found that 17 of 72 (23%) were diagnosed with EoE [7]. In contrast, studies in adult populations have reported lower prevalence rates of EoE, ranging from 3% to 6% [8–11]. However, these studies were limited by their small sample sizes and heterogeneous study designs.

The higher prevalence of atypical symptoms after the diagnosis of EoE may reflect multiple pathophysiological mechanisms. Esophageal inflammation and impaired barrier function may increase esophageal sensitivity and facilitate the perception of extraesophageal symptoms. In addition, increased medical surveillance following an EoE diagnosis may also lead to improved recognition and reporting of atypical symptoms. Further prospective studies using standardized symptom assessment and objective reflux monitoring are needed to better clarify these associations.

To the best of our knowledge, no existing data specifically address GERD symptoms in patients with EoE. In our cohort, we demonstrated a high proportion of patients experiencing both typical and atypical GERD symptoms. Interestingly, typical GERD symptoms were more prevalent before EoE diagnosis (24.8%), whereas atypical symptoms predominated afterward (28%). This shift may reflect the complex interplay between these conditions, with bidirectional interactions influencing their symptomatology. Chronic EoE may affect esophageal motility, leading to a higher incidence of atypical GERD symptoms after diagnosis. Additionally, patients with typical GERD symptoms before their EoE diagnosis may initially have had refractory GERD that was later correctly identified as EoE.

The findings of our study indicate that following an EoE diagnosis, certain GERD symptoms-particularly cough and other atypical manifestations, became more prevalent, accompanied by increased use of proton pump inhibitors (PPIs).

Furthermore, allergic rhinitis/sinusitis and hiatal hernia were independent predictors of typical GERD symptoms among patients with EoE, whereas asthma, food allergy, and eosinophil counts ≥ 500 were independent predictors of atypical GERD symptoms. Hiatal hernia is a well-recognized risk factor in GERD pathophysiology. Previous studies have reported a frequency rate of 45.3% and 38.7% for hiatal hernia among patients who underwent upper endoscopy for reflux symptoms [12,13], and hiatal hernia was more common in females than in males [14], whereas most patients in our EoE cohort were male. Anatomic changes related to hiatal hernia can disrupt the integrity of the anti-reflux barrier, resulting in increased acid exposure, which most directly produces heartburn and regurgitation. Allergic rhinitis/sinusitis may be a predictor of GERD symptoms by sharing an atopic diathesis that promotes mucosal inflammation along the aerodigestive tract. Postnasal drainage and chronic oropharyngeal inflammation can lower esophageal sensory thresholds, thereby amplifying the perception of reflux. In agreement with our findings, a previous study reported an adjusted hazard ratio of 1.94 for GERD among patients with allergic rhinitis [15].

Asthma, food allergy, and eosinophilia were associated with an increased risk of atypical GERD symptoms in our cohort. The relationship between reflux and asthma is well recognized as bidirectional; micro aspiration and acid reflux can trigger bronchospasm, whereas coughing raises transdiaphragmatic pressure and promotes reflux. Moreover, atopic conditions, including food allergy and eosinophilia, may contribute to esophageal–laryngeal hypersensitivity, resulting in

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atypical GERD symptoms. In addition, chronic cough may be related to GERD with complex pathophysiology. The pathogenesis of GERD-related chronic cough (GERC) is multifactorial and mainly involves reflux theory (acid reflux, micro aspiration, and airway reflux), reflex theory (acid reflex), and esophageal dysmotility [16].

In summary, previous studies have explored the coexistence of GERD and EoE, particularly among patients with refractory reflux symptoms, and only small part of GERD patients were diagnosed with EoE, in a prospective study only one of 103 patients with PPI refractory GERD patients, was diagnosed with EoE [17]. Data specifically evaluating the prevalence, temporal patterns, and predictors of typical and atypical GERD symptoms in large population-based cohorts of patients with established EoE are limited. In the present study, we found that GERD is prevalent among patients with EoE, and the substantial clinical and histological overlap between these conditions presents significant diagnostic and therapeutic challenges for clinicians. Both disorders can manifest similar symptoms; however, our findings demonstrate that typical symptoms are more common before the diagnosis of EoE, whereas atypical GERD symptoms tend to emerge thereafter. The true relationship and interaction between these two diseases warrant further prospective investigations

Clinicians should be aware of the high prevalence of GERD symptoms among patients with EoE, particularly the predominance of typical GERD symptoms before the diagnosis of EoE. EoE should be considered in patients with PPI-refractory GERD and those with hiatal hernia or allergic rhinitis, prompting early diagnostic evaluation and targeted management. Importantly, atypical GERD symptoms, especially in patients with comorbid airway or laryngeal hypersensitivity, become more common after EoE diagnosis, underscoring the need for a comprehensive assessment. A high index of suspicion for EoE should be maintained in patients presenting with refractory GERD symptoms or atypical presentations, particularly with a history of atopy. These observations underscore the importance of a comprehensive and multifaceted approach for the diagnosis of EoE, including symptom assessment, targeted esophageal biopsies, and exclusion of other conditions [18].

The strengths of this study include its large sample size and population-based design, which enhance the generalizability of the findings. To our knowledge, this is the first comprehensive investigation of the frequency and symptomatology of GERD in patients with EoE. This study has several limitations. The retrospective design of this study is a key limitation. The diagnoses of EoE and GERD in the national cohort were based solely on ICD-9/10 codes without histopathological or functional validation, which may have introduced symptom misclassification, and overlap with respiratory or functional disorders cannot be excluded. Additionally, symptom-based GERD classification is limited, particularly in the absence of pH-impedance testing.

Conclusions

This study demonstrated a high prevalence and overlap of gastroesophageal reflux disease (GERD) among patients with eosinophilic esophagitis (EoE). Typical GERD symptoms were more common before EoE diagnosis, whereas atypical symptoms increased thereafter. These findings suggest that reflux evaluation should prioritize anatomical causes, and that concurrent management of EoE and atopy should be considered for patients presenting with atypical GERD symptoms.

Author Contributions: S. E. and N. A. F. conceived and designed the study. R.S.S. and N. A. F. collected the data. S.E., J.I, M.A.T., M.A.A., O.S., and N.A.F. analyzed and interpreted the data of the study. S.E. and N.A.F. drafted the manuscript. All authors have read and approved the final manuscript.

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Institutional Review Board Statement: the study was conducted in accordance with the declaration of Helsinki, and approved by the Ethics committee of Soroka University Medical Center (protocol code 0057-25-SOR).

Informed Consent Statement: Patient consent was waived due to the retrospective design of the study and the anonymity of the patients.

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Conflicts of Interest: The authors declare that there is no conflict of interests in this study.

Abbreviations.

The following abbreviations are used in this manuscript:

EoE Eosinphilic Esophagitis
GERD Gastroesophageal reflux disease
PPI Proton pump inhibitors

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