

Identification of Clinical and Laboratory Markers for Predicting Eosinophilic Esophagitis in Adults

Ulrike von Arnim^a Thomas Wex^a Friedrich-W. Röhl^b Helmut Neumann^a
Dörthe Küster^c Jochen Weigt^a Klaus Mönkemüller^a Peter Malfertheiner^a

^aDepartment of Gastroenterology, Hepatology and Infectious Diseases, and Institutes of ^bBiometrics and Medical Informatics, and ^cPathology, Otto von Guericke University, Magdeburg, Germany

Key Words

Eosinophilic esophagitis · Gastroesophageal reflux disease · Pre-endoscopic marker constellation

Abstract

Background: The diagnosis of eosinophilic esophagitis (EoE) and differentiation from gastroesophageal reflux disease (GERD) is potentially challenging and is based upon clinical signs and endoscopic and histological features. In order to alert the endoscopist to consider EoE in patients with esophageal symptoms before performing esophagogastroduodenoscopy, we aimed to identify a set of clinical and laboratory markers for predicting EoE. **Methods:** The study included 43 patients with either EoE (n = 23) or GERD (n = 20). The diagnosis of EoE was based on International Consensus Criteria. Age, gender, weight loss, history of atopy, dysphagia, history of food impaction, proton pump inhibitor (PPI) refractory heartburn, odynophagia, peripheral eosinophilia, and serum IgE were analyzed. Each symptom or sign was classified as '0' (absent, normal) or '1' (present, elevated), individually analyzed and statistically evaluated among the two groups of patients. Logistic regression analysis was carried out to identify a clinically applicable marker constellation to differentiate EoE from GERD. **Results:** Univariate analysis identified 6 out of the 10 variables to be significant between both groups. A stepwise procedure of logistic regression led to a model in which 3 out of the initial 10 items were found to be

relevant for differentiating GERD and EoE. Derived from this model, an optimal differentiation was achieved by using the following simplified equation: peripheral eosinophilia + history of food impaction + PPI refractory heartburn leading to a maximal value of 3 (1 + 1 + 1). Based on a cut-off value of ≥ 2 , sensitivity and specificity for diagnosing EoE were 91 and 100%, respectively. **Conclusion:** A defined set of markers including two clinical features and one laboratory parameter is highly predictive of EoE and thus allows physicians to distinguish EoE from GERD even before upper gastrointestinal endoscopy is performed.

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Introduction

Eosinophilic esophagitis (EoE) is an emerging clinico-pathologic condition with a rapidly increasing prevalence [1, 2]. EoE is defined as a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by predominant eosinophilic inflammation of the esophageal mucosa [3] (>15 eosinophils per high-power field). Other regions of the upper gastrointestinal tract are usually not affected.

Clinically, adults suffering from EoE present with symptoms such as dysphagia for solids [4, 5], retrosternal/chest pain or 'refractory' heartburn and food impaction

Table 1. Demographic data of patients stratified to the clinical diagnosis

Variable	EoE (n = 23)	GERD (n = 20)	p value (Fisher's test or t test)
Male/female	16/7 (69.6%)	11/9 (55.0%)	0.361
Mean age $\pm$ SD (range), years	40.26 $\pm$ 14.42 (24–69)	56.31 $\pm$ 16.2 (19–86)	0.002
PPI medication ¹	20/21 ²	18/19 ³	0.585

¹ Two weeks prior to diagnosis or anamestic treatment trial. ² Data not available for 2 patients. ³ Data not available for 1 patient.

[6, 7]. However, other disorders such as gastroesophageal reflux disease (GERD) can present with similar symptoms [3, 7]. The first case of EoE was reported in a patient with vigorous achalasia [9].

Since clinical suspicion of EoE requires histological confirmation, esophageal biopsies are mandatory [3, 8]. The endoscopic features of EoE are variable ranging from subtle mucosal changes to the 'characteristic' signs such as longitudinal furrows, white Candida-like speckles, crêpe paper mucosa, small-caliber esophagus, longitudinal shearing, friability, edema and ringed esophagus (i.e. 'feline esophagus') [10–13]. However, endoscopic findings are neither specific for EoE nor present in all individuals with EoE [8–14]. In a careful study of endoscopic features of EoE, 42% of patients with EoE did not present the 'classical' endoscopic features [14] which underline the need for obtaining a sufficient number of biopsies for histological confirmation of EoE [8–14]. In routine practice a missed histopathological investigation leads to a significant delay in the diagnosis of EoE [15, 16].

The aim of this study was to evaluate various clinical and laboratory values, and to identify a simple, clinically applicable, marker set that could predict the presence of EoE and thus alert the endoscopist performing endoscopy to pay additional attention to esophagus mucosal examination, including the retrieval of sufficient biopsies to rule in or out the diagnosis of EoE.

Materials and Methods

The study was conducted and carried out in accordance and approval of the local ethical committee of Otto von Guericke University, Magdeburg, Germany.

Patients

Patients (>18 years old) were enrolled at our outpatient department between December 2005 and May 2007, retrospectively (EoE n = 11, GERD n = 8), and from June 2007 and March 2010, prospectively (EoE n = 12, GERD n = 10).

Table 2. Clinical and laboratory parameters stratified to the clinical diagnosis

Signs/symptoms	EoE (n = 23)	GERD (n = 20)	p value
Weight loss	1	3	0.324
History of atopy	18	5	0.001
History of food impaction	20	2	<0.001
PPI refractory heartburn	18	4	<0.001
Dysphagia	21	4	<0.001
Odynophagia	3	0	0.236
IgE elevation	19	2	<0.001
Peripheral eosinophilia	19	0	<0.001

Primary data were binary coded as positive or negative as described in Materials and Methods. Data present the proportion of positive findings in the subgroup, and were analyzed by Fisher's exact test (p values below the significance level are in bold face).

Patients with typical reflux lesions were grouped in GERD as erosive reflux disease (ERD), patients without endoscopic lesions but typical reflux symptoms underwent a 24-hour pH-combined esophagogastrophic pH-metry. Patients with a pathologic 24-hour pH-metry were also grouped to GERD and classified as non-erosive reflux disease (NERD). A pathologic 24-hour pH-metry was defined as pH <4 for 4.5% of the time and a DeMeester score of >14.9. Patients with a known history of Crohn's disease, celiac disease, coagulopathy or thrombocytopenia, liver cirrhosis with esophageal varices and pregnant women were excluded.

Patient Interview and Questionnaire

Every patient underwent a detailed history and physical examination. In particular, severity and frequency of dyspeptic symptoms, weight loss (>5 kg/3 months), history of atopy (seasonal allergies, rhinoconjunctivitis, hay fever, asthma, food allergies, atopic dermatitis) history of prior food impactions, response or refractoriness to proton pump inhibitor (PPI) medication (PPI refractory heartburn), and odynophagia were documented. The questionnaire further included age and gender. Data were binary-coded and noted as positive/present/elevated (1) or negative/absent/normal (0) (tables 1, 2).

Laboratory Analysis

Blood leukocyte count and a manual differential were performed in every patient. The normal value for eosinophils in our laboratory is 0.00–0.05%, for a better consensus we used >300–350/mm³ according to recommendations [3]. Immunoglobulin E (IgE) serum levels were considered elevated when >100 IU/ml.

Endoscopy

Esophagogastroduodenoscopy was performed in every patient by the consulting gastroenterologist under conscious sedation using midazolam 5 mg administered as an intravenous bolus with a standard videogastroscope (GIFQ 160 or 145; Olympus Optical Europe, Hamburg, Germany). All patients provided verbal and written informed consent for endoscopy. A total of up to 6 biopsies were obtained routinely from three different parts of the esophagus. The distal esophagus was defined as 5 cm above the Z-line (2 biopsies), mid-esophagus was defined as 10–20 cm above the Z-line, and proximal esophagus 20 cm and more above the Z-line. Gross esophageal findings were biopsied separately, e.g. whitish plaques, furrows or other mucosal lesions noted by the endoscopist. The Los Angeles Classification was used to describe and grade erosive esophagitis.

Specimens were placed in separate vials indicating their origin (e.g. distal, mid and proximal esophagus or specific lesion). Gastric (1× antrum, 1× corpus) and duodenal (2×) biopsies were obtained routinely to exclude eosinophilic gastroenteritis. A standard biopsy forceps was used to obtain the biopsies.

Pathology

The formalin-fixed biopsies were routinely processed, paraffin-embedded and stained with hematoxylin and eosin, PAS and modified Giemsa stain, and histologically examined using standard light microscopy. The pattern of gastritis was evaluated by the updated Sydney System [17]. Gastroesophageal reflux-associated esophagitis was excluded using the Ismail-Beigi criteria [18] modified by Vieth et al. [19]. According to Collins [20], EoE was diagnosed based on major features such as increased intraepithelial eosinophils (≥ 15 per high-power field of 0.55 mm² in areas of peak density), eosinophilic microabscesses, aggregates of eosinophils in the epithelial surface layers, degranulation of eosinophils, and surface sloughing of epithelial cells and eosinophils in ≥ 2 biopsies (levels).

Statistical Analysis

Data were analyzed using SPSS software version 17 (SPSS Inc., Chicago, Ill., USA). Age is presented as mean $\pm$ SD; qualitative parameters are presented as relation between positive and negative proportions. The Welch-Satterthwaite t test was used for age comparison and Fisher's exact test was used for binary-coded variables. The development of the scoring system was performed in a two-step approach. In the first step, univariate methods were used to evaluate which of the 10 variables contributed to the differentiation between both groups. In a second step, a subset of explanatory variables was identified by logistic regression using the LR statistic of the model-selection method. Finally, a simple and practicable symptom/sign constellation was constructed from the regression function. The performance of this model was evaluated by calculating error rates. All statistical decisions were made two-tailed with a critical probability of $\alpha = 5\%$ without α adjustment for univariate tests.

Table 3. Patient classification models, including a model correctly classifying patients using three clinical and laboratory parameters

Model	EoE (n = 23)	GERD (n = 20)
Logistic regression with 10 parameters	23 (100%)	20 (100%)
Logistic regression with parameter selection (3 parameters) ¹	22 (95.7%)	20 (100%)
Three marker set (marker constellation) ²	21 (91.3%)	20 (100%)

¹ Peripheral eosinophilia, history of food impaction, PPI refractory heartburn. ² Marker constellation = peripheral eosinophilia + history of food impaction + PPI refractory heartburn.

Results

The analysis of demographic data revealed a higher tendency for male gender in EoE ($p = 0.361$) and younger age were more prevalent in patients with EoE compared to those having GERD ($p = 0.002$). The use of PPI medication prior to or by anamnesis at time of diagnosis was not significantly different in both groups ($p < 0.585$; table 1).

Looking for additional parameters for differentiating these two diseases, the following eight clinical or laboratory parameters were studied: weight loss, history of atopy, history of food impaction, PPI refractory heartburn, dysphagia, odynophagia and peripheral eosinophilia, and elevated IgE (table 2). As illustrated in table 2, six of these parameters allowed a reliable univariate differentiation of EoE versus GERD.

In order to achieve optimal diagnostic sensitivity and specificity, a logistic regression analysis was performed using all eight parameters (table 2) analyzed including gender and age (table 1). The additional stepwise procedure for parameter reduction showed that a simple marker constellation was achieved based on three parameters to differentiate EoE from GERD (table 3). The proportion of correctly classified observations of the validation procedure is illustrated in table 4. Based on this analysis, the following equation achieving optimal scoring was identified by rounding and weighting the factors of the regression function:

Suspicion of EoE = peripheral eosinophilia + food impaction + PPI refractory heartburn.

Total values from binary coding (see Materials and Methods) range between 0 and 3 (= 1 + 1 + 1). Using a cut-off level of ≥ 2 for predicting EoE, 21 out of 23 pa-

Table 4. Stratification of patients of the two groups in relation to the proposed marker set

Sum marker set	EoE (n = 23)	GERD (n = 20)	
0	0	14	Sensitivity 91%
1	2	6	
2	10	0	Specificity 100%
3	11	0	

tients with EoE and all GERD patients were correctly identified (table 4). The sensitivity and specificity was 91 and 100% respectively, leading to an overall correct diagnosis of EoE in 95.35% of all patients (table 4).

Discussion

Here, we describe a pre-endoscopically available marker constellation that might be suitable for detection of EoE and differentiation from GERD in adult patients. Using this marker combination allows the strong suspicion (or reasonable suspicion) of EoE with high accuracy before performing esophagogastroduodenoscopy and directs the gastroenterologist to take a sufficient number of biopsies from the esophagus – even if ‘typical endoscopic signs’ of EoE are missing – for confirmation of EoE.

The clinical symptoms of EoE vary with the age of the patient. Symptoms in children with EoE are predominantly abdominal pain, failure to thrive, vomiting and gastroesophageal reflux-like symptoms [21]. A study in pediatric patients showed that dysphagia and anorexia/early satiety could identify children with EoE in contrast to GERD patients [22].

The predominant symptoms of EoE in adult patients are solid-food dysphagia, chest pain and food impaction [3, 23, 24]. Recurrent or sporadic food impactions for years are often reported by patients before the confirmed diagnosis of EoE [25]. EoE was reported as the underlying cause of food impaction in 50% of the cases [6]. However, the aspect of a history food impaction predicting EoE has not been studied before. Indeed, our findings suggest that the past medical history of food impaction is the most relevant clinical symptom of EoE as 20 of 23 presented with this symptom at some time prior to diagnosis.

The presence of PPI refractory heartburn was another strong predictor for the differentiation between GERD and EoE patients. This finding is consistent with require-

ments for diagnosing EoE as recommended by consensus recommendations [8]. New recommendations [3] define a subgroup of patients that have (a) EoE symptoms, (b) diagnostic exclusion of GERD, and (c) clinicopathologic PPI responsiveness. These patients are classified as ‘PPI-responsive esophageal eosinophilia’ or ‘PPI-responsive EoE’. In our EoE cohort we could not identify a patient belonging to this subgroup since all patients had diagnostic exclusion of GERD and failed PPI treatment trial (either 2 weeks before or at the time of anamnesis or prior to diagnosis).

EoE is associated with atopic diseases such as asthma, rhinoconjunctivitis, hay fever, atopic dermatitis and allergic diseases of the airways [8] and approximately 70% of patients suffering from EoE have a positive history of atopic disease [7, 26] and present elevated IgE levels and peripheral eosinophilia [9, 27]. Our findings are in line with these studies, and support the concept that the presence of atopy and consecutive associated peripheral eosinophilia represent a differential marker between EoE and patients with GERD. Nevertheless, as also seen in our study, patients with GERD can also have a history of atopy, but none of them presented with peripheral eosinophilia. With the exception of odynophagia and weight loss, the other 6 variables significantly correlated with each other. Thus, it makes sense to try to simplify the diagnosis by attempting the most simple marker constellation.

Taking advantage of multiple clinical parameters, an easily accessible set of markers was established that alerts the gastroenterologist on the possibility of underlying EoE and encourages to examine the esophagus very carefully during endoscopy and to take sufficient biopsies from different mucosal areas. Although it is recommended to take esophageal biopsies in patients with symptoms of dysphagia, very often these samples are not obtained in clinical practice. Due to the missing histological evaluation at initial endoscopy, diagnosing of EoE often is frequently delayed. Using the identified marker set of this study or potentially other combinatory approaches will most likely help to identify EoE earlier and to shorten the diagnostic period, which can range from 0 to 180 months [15, 16]. Another potential advantage may be an increased cost-effectiveness utility of endoscopy in patients with a substantiated suspicion of EoE and can help to justify the clinically relevant choices for esophageal biopsies.

Our study has potential limitations. First, this is a single-center, tertiary care-based study leading to potential selection bias. However, the diagnosis of EoE was based on accepted consensus criteria which should apply to any setting, including primary care. Indeed, this strengthens the

results of our data, as the diagnosis of EoE was strict and thus the proposed set of markers may be more solid. Second, the number of patients with EoE may be falsely inflated. Nonetheless, this should increase the validity of our results as all patients were carefully diagnosed using functional methods and standard criteria. Third, the number of patients is relatively low, which, from the statistical point of view, can lead to 'over-fitting'. Moreover, this can only be solved by performing a multicenter study. Lastly, we assessed for presence of atopy based on history and peripheral eosinophilia, but not using skin or prick testing. Nevertheless, this may just add to the validity of the identified marker constellation and one could be tempted to hypothesize that if skin prick further substantiates the diagnosis of EoE, in the future EoE could be mainly diagnosed using clinical, laboratory and allergic test criteria.

In conclusion, the identified set of markers, including two clinical parameters (history of food impaction, no clinical response to prior PPI treatment) and one laboratory test (peripheral eosinophilia), was capable of differentiating EoE from GERD with a high accuracy. Based on our findings, we propose that this set of markers should be prospectively evaluated in a diagnostic algorithm of EoE to study its diagnostic relevance. If confirmed in larger multicenter studies for example, this would lead to an early diagnosis and consecutively earlier treatment of EoE.

Disclosure Statement

None of the authors have any conflicts of interest to declare. No financial support was received to conduct this study.

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