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Eosinophilic Oesophagitis and Proton Pump Inhibitor-Responsive Oesophageal Eosinophilia Have Similar Clinical, Endoscopic and Histological Findings

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Abstract and Introduction

Abstract

Background Some patients with a phenotypic appearance of eosinophilic oesophagitis (EoE) respond histologically to PPI, and are described as having PPI-responsive oesophageal eosinophilia (PPI-REE). It is unclear if PPI-REE is a GERD-related phenomenon, a subtype of EoE, or a completely unique entity.

Aim To compare demographic, clinical and histological features of EoE and PPI-REE.

Methods Two databases were reviewed from the Walter Reed and Swiss EoE databases. Patients were stratified into two groups, EoE and PPI-REE, based on recent EoE consensus guidelines. Response to PPI was defined as achieving less than 15 eos/hpf and a 50% decrease from baseline following at least a 6-week course of treatment.

Results One hundred and three patients were identified (63 EoE and 40 PPI-REE; mean age 40.2 years, 75% male and 89% Caucasian). The two cohorts had similar dysphagia (97% vs. 100%, P = 0.520), food impaction (43% vs. 35%, P = 0.536), and heartburn (33% vs. 32%, P= 1.000) and a similar duration of symptoms (6.0 years vs. 5.8 years, P= 0.850). Endoscopic features were also similar between EoE and PPI-REE; rings (68% vs. 68%, P = 1.000), furrows (70% vs. 70%, P = 1.000), plaques (19% vs. 10%, P = 0.272), strictures (49% vs. 30%, P = 0.066). EoE and PPI-REE were similar in the number of proximal (39 eos/hpf vs. 38 eos/hpf, P = 0.919) and distal eosinophils (50 vs. 43 eos/hpf, P = 0.285).

Conclusions EoE and PPI-responsive oesophageal eosinophilia are similar in clinical, histological and endoscopic features and therefore are indistinguishable without a PPI trial. Further studies are needed to determine why a subset of patients with oesophageal eosinophilia respond to PPI.

Introduction

The presence of dense eosinophilia on oesophageal biopsies, especially in the setting of dysphagia and food impaction, suggests a diagnosis of eosinophilic oesophagitis (EoE). This increasingly recognised entity has emerged as the most common cause of dysphagia in adults.[1] According to the most recent consensus guidelines, a trial of acid-suppressants must be administered prior to establishing a diagnosis of EoE.[2] This is primarily to rule out gastro-oesophageal reflux disease (GERD), a common condition that can also result in dense oesophageal eosinophilia. Although previously believed to cause only mild eosinophilia, studies have demonstrated that GERD may also lead to dense eosinophilic infiltration on oesophageal biopsies similar to what is observed in EoE.[3,4] Interestingly, since the publication of the latest consensus guidelines, it has become more apparent that some patients with a phenotypic appearance of EoE and distinct from GERD (i.e. dysphagia, history of atopy, rings/furrows/plaques on endoscopy and dense eosinophilia on biopsies) respond histologically to proton pump inhibitors (PPI).[5] These patients are described as having PPI-responsive oesophageal eosinophilia (PPI-REE), to distinguish them from EoE patients. To date, it is unclear if PPI-REE represents a GERD-related phenomenon, a subtype of EoE, or a completely unique entity.[6–9] The aim of this study was to compare the demographic, clinical, endoscopic and histological features of EoE and PPI-REE in a population of patients from two institutions.

Methods

Study Design

Two separate databases were reviewed from 2011 to 2012, which included patients from Walter Reed National Military Medical Center and the Swiss EoE database (SEED). Review was limited to after 2011 to include only patients diagnosed per latest EoE consensus statement. Data from the two institutions, who share similar methods in monitoring EoE patients with established registries, were combined to increase the total sample size of the study. All adult patients (≥18 years of age) were consecutively enrolled in their respective registries. Patients were stratified into two groups: EoE and PPI-REE. EoE was defined by the most recent consensus guidelines: clinically by symptoms of oesophageal dysfunction, histologically by the presence of at least 15 eos/hpf on oesophageal biopsies and a lack of response to a course of PPI treatment.[2] PPI-REE was defined as presenting with similar clinical symptoms as EoE yet achieving less than 15 eosinophils eos/hpf and a 50% decrease from baseline following at least a 6-week course of twice-daily PPI treatment.

Data Collection

For each patient, data on demographics (race, age, gender), clinical presentation (dysphagia, food impaction, heartburn), duration of symptoms, endoscopic features (rings, furrows, plaques, strictures, Schatzki's rings, presence of erosive oesophagitis) and whether dilation had been performed were collected. If available, results of a 24-h pH study were also recorded. GERD was defined when % total time pH <4 was greater than 4.2% time of the study period. Coexisting atopy and allergy history (allergic rhinitis, asthma, food allergies, and seasonal allergies) and histological features (peak proximal and peak distal eosinophils count) were also obtained from the databases and electronic medical records.

Statistical Analysis

Data were collated and analysed using statistical software spss version 16 (Statistical Package for the Social Sciences, Chicago, IL, USA). Data for categorical variables are expressed as proportions and percentages and data for continuous variables are expressed as means and standard deviations. Between-group comparisons of demographic, clinical and endoscopic variables were analysed with Fisher's exact test for categorical variables, and student's independent *t*-test for continuous variables. A *P*-value of less than 0.05 was considered statistically significant.

Results

A total of 103 patients were included in the study (63 EoE and 40 PPI-REE; mean age 40.2 years ± 12.9, 75% male, and 89% Caucasian). There were 66 patients from Walter Reed and 37 from SEED. In comparing patients between the two institutions, Walter Reed patients were slightly older in age (42 years ± 12 vs. 36 years ± 13, $P = 0.024$) and reported symptoms for a longer period of time (92 months ± 76 vs. 35 months ± 23, $P < 0.001$). The groups were similar in gender (% male: 74% vs. 76%, $P = 0.535$), race (% Caucasian: 88% vs. 92%, $P = 0.641$) and proportion of patients with PPI-REE (36% vs. 43%, $P = 0.316$). All the patients in the Walter Reed cohort were treated with Esomeprazole 40 mg twice daily. In the Swiss cohort, 26 patients were treated with Esomeprazole 40 mg twice daily and 13 with Pantoprazole 40 mg twice daily. Clinical presentation and histological features were similar between the two institutions. With regard to endoscopic features, concentric rings and longitudinal furrows were similar between the two study sites; however, white plaques (27% vs. 9%, $P = 0.018$) and strictures (62% vs. 30%, $P = 0.003$) were more common in Swiss patients.

Within the entire study cohort, there was no significant difference in demographics between EoE and PPI-REE (age 40 years ± 13 vs. 41 years ± 12, $P = 0.767$; male 81% vs. 65%, $P = 0.102$; Caucasian 91% vs. 88%, $P = 0.436$). Among the 16 patients with PPI-REE who underwent 24 h pH monitoring, no patients had GERD. The two cohorts were similar regarding the presentation of dysphagia (97% vs. 100%, $P = 0.520$), food impaction (43% vs. 35%, $P = 0.536$) and heartburn (33% vs. 32%, $P = 1.000$). Duration of symptoms was similar between EoE and PPI-REE (6.0 years vs. 5.8 years, $P = 0.850$) (). With regard to atopic history, EoE patients had significantly less allergic rhinitis compared with PPI-REE (36% vs. 58%, $P = 0.041$). However, the cohorts were similar in asthma (29% vs. 30%, $P = 1.000$), food allergies (35% vs. 42%, $P = 0.533$) and eczema (13% vs. 15%, $P = 0.774$).

Table 1. There were no significant differences in any of the clinical or endoscopic characteristics between EoE and PPI-REE patients

	EoE *N* = 63	PPI-REE *N* = 40	*P*-value
Clinical presentation			
Dysphagia	97%	100%	0.520
Food impaction	43%	35%	1.000
Heartburn	33%	32%	1.000
Endoscopic findings			
Rings	68%	68%	1.000
Furrows	70%	70%	1.000
Plaques	19%	10%	0.272
Strictures	49%	30%	0.066
% Dilation	54%	43%	0.314

Endoscopic features were also similar between EoE and PPI-REE (Figure 1), including concentric rings (68% vs. 68%, *P* = 1.000), longitudinal furrows (70% vs. 70%, *P* = 1.000), white plaques (19% vs. 10%, *P* = 0.272), strictures (49% vs. 30%, *P* = 0.066), Schatzki's rings (27% vs. 40%, *P* = 0.197) and erosive oesophagitis (14% vs. 13%, *P* = 1.000). Dilation was performed in 54% of EoE vs. 43% of PPI-REE patients, *P* = 0.314). No complications from dilation occurred in any patient. EoE and PPI-REE were similar in the number of proximal (39 ± 36 eos/hpf vs. 38 ± 23 eos/hpf, *P* = 0.919) and distal eosinophils (50 ± 32 vs. 43 ± 28 eos/hpf, *P* = 0.285).

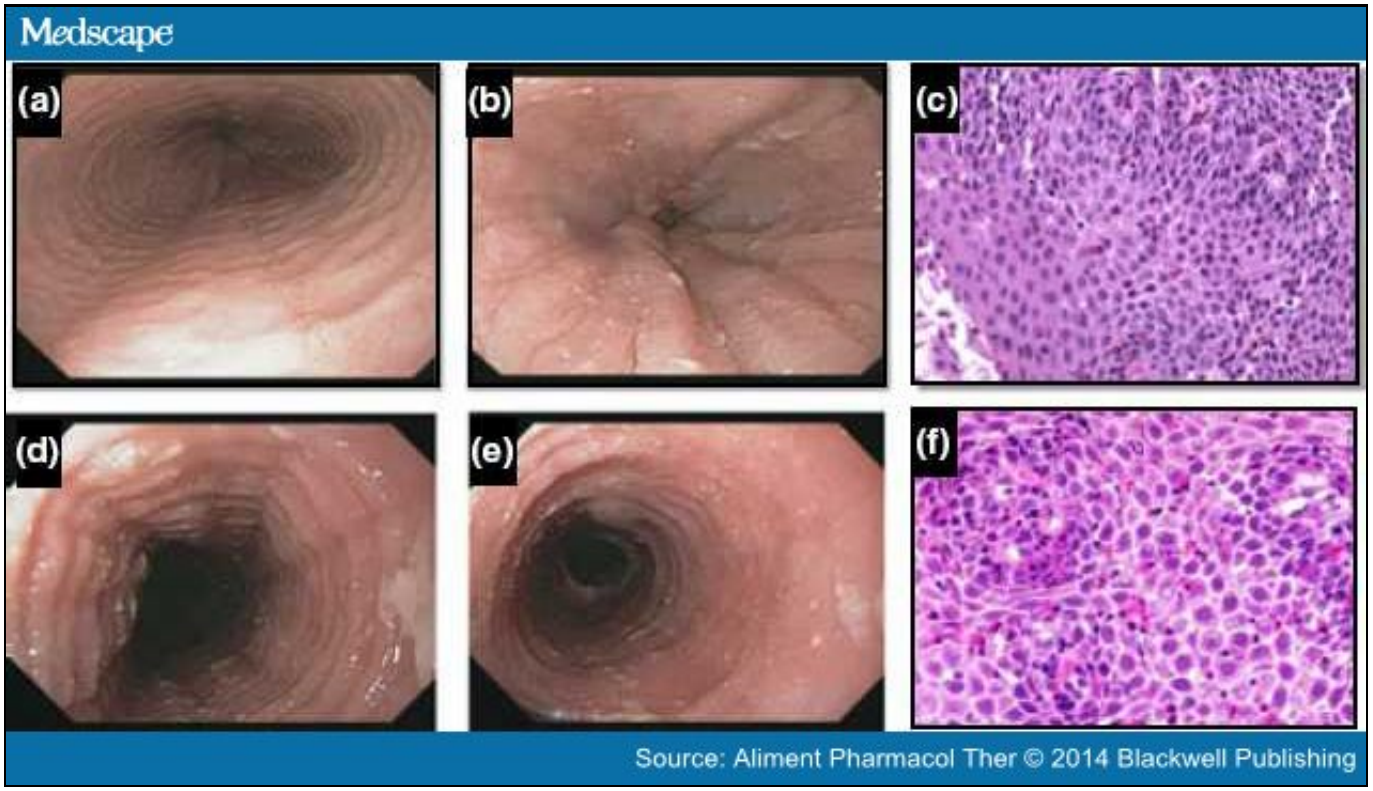

Figure 1.

Example of EoE and PPI-REE cases. This EoE patient demonstrated concentric rings (a), white plaques (b), and dense eosinophilia (c), which persisted following an 8-week course of PPI. This PPI-REE patient had concentric rings (d), white plaques (e) and dense eosinophilia, which resolved following a course of PPI therapy.

Discussion

EoE is an increasingly recognised entity, which has become the leading cause of dysphagia.[10] The clinical presentation and endoscopic features are often dramatic and gastroenterologists may initiate treatment with topical steroids prior to a course of PPIs,[11] a step necessary to establish the diagnosis of EoE.[2,5] Our study demonstrates that EoE and PPI-REE are indistinguishable without a PPI trial with regard to clinical presentation, endoscopic findings and histology based on data from two study sites. Furthermore, many patients with suspected EoE may respond to PPI, therefore obviating the need for topical steroids and specialised diets.[12]

PPI-REE is a newly described entity initially reported in 3 paediatric patients with suspected EoE who achieved clinical and histological response to an 8-week course of twice daily omeprazole.[13] Although PPI was not considered primary therapy for EoE in the initial guidelines,[14] it appeared that many children and adults with this condition reported improvement in symptoms. Additionally, histological response to PPI became more apparent in patients presenting with typical EoE symptoms and endoscopic findings, as well as having marked levels of eosinophils on biopsies. Therefore, the term PPI-REE was recognised in the latest expert consensus statement.[2] What remains unclear is whether this entity should be defined clinically, histologically, or requires both criteria.

Clinical response to PPI in EoE patients has been described in multiple studies; however, several of these studies were performed prior to the latest consensus statement and may have included PPI-REE patients. In one study, nearly 50% of adult patients presenting with a food impaction and having dense eosinophilia on oesophageal biopsies reported clinical improvement with acid suppression.[15] Similar results to a PPI were demonstrated in children with significant oesophageal eosinophilia despite a negative pH study.[16] Notably, in a recent study, baseline pH testing was not predictive of PPI response.[17]

Even more intriguing than achieving clinical response in suspected EoE patients is the presence of histological response, especially in the absence of classic reflux symptoms, negative pH testing and absence of erosive oesophagitis on endoscopy. To date, several prospective studies have reported such findings.[6,9,18,19] In one randomised controlled trial, histological response was achieved in approximately one-third of patients with suspected EoE with once-daily PPI for 8 weeks.[6] Another prospective study reported a 50% response in patients with an EoE phenotype after treatment with twice daily PPI.[18] In 60 adult patients presenting with symptoms of oesophageal dysfunction and dense oesophageal eosinophilia treated with twice-daily PPI for 8 weeks, histological improvement was demonstrated in more than 50% of the cohort to include more than one-third achieving complete resolution.[19] When stratified by symptom profile (GERD vs. EoE), there was no significant difference in response to PPI. In other words, patients with suspected EoE achieved a similar response to PPI compared with patients presenting with GERD symptoms. Most recently, in a prospective study evaluating the prevalence of PPI-REE, response to PPI was seen in one-third (24/66) of patients presenting with dysphagia and marked oesophageal eosinophilia.[9]

Several theories exist to explain the mechanism behind PPI response in oesophageal eosinophilia. First, PPIs can heal a disrupted epithelial barrier and normalise intercellular spaces, thereby preventing the permeability of food allergens.[20,21] This theory would support that PPI-REE may be a subset of GERD. It remains unclear, however, why patients with physiological oesophageal acid exposure on pH studies would develop such a degree of damage to promote antigen exposure. Another theory can be attributed to anti-inflammatory properties of PPI, independent of acid inhibition. PPIs have been shown to exhibit anti-inflammatory properties by acting directly on principal cytokines (IL-4 and IL-13) involved in the recruitment of eosinophils in the oesophagus.[22] Recently, omeparazole was shown to block the expression of TH_2 cytokine-stimulated expression of eotaxin-3 in cultures from GERD and EoE patients.[23] Additionally, in one study, treatment with a PPI reduced levels of eotaxin-3 and TH_2 cytokines in PPI-REE patients similar to what was observed in EoE following treatment with topical steroids.[24] This is suggestive of PPI-REE representing a subset of EoE patients who respond to PPI. The reason why some patients respond and others do not needs to be further explored. Interestingly, two studies in children raised questions whether PPI responsiveness may represent a transient phenomenon and dense eosinophilia may recur over time.[25] Larger studies are currently underway to address this observation.

Strengths of this study include combining data from two institutions which have comprehensive EoE registries. Patients were generally homogenous between the study sites and there was a similar proportion of PPI-REE patients between the two centres. However, there were some differences between patients of the two study sites.

For instance, mean duration of symptoms was longer and was more variable in Walter Reed patients, while white plaques and strictures were more common among Swiss patients. These differences did not affect the results of the combined data as there were no significant differences between EoE and PPI-REE patients in duration of symptoms, white plaques and strictures within each study site. Limitations of this study include its retrospective design and the lack of a validated definition of PPI-REE. We chose to combine an absolute number of eosinophils as less than 15 eos/hpf and a decrease of 50% from baseline. This definition was to ensure that there was a significant change in eosinophils count from baseline.

In conclusion, the results of this study demonstrate that EoE and PPI-REE are similar in clinical, histological and endoscopic features and therefore cannot be distinguished without a PPI trial. Further studies are needed to determine why a subset of patients with oesophageal eosinophilia respond to PPI.

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Authorship

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Author contributions

Fouad J. Moawad, Alain Schoepfer: study concept and design, subject recruitment, maintaining database, analysis and interpretation of data, drafting of manuscript. Ekaterina Safroneeva, Mazer Ally, Yen-Ju Chen: subject recruitment, maintaining database, drafting of the manuscript. Corinne L. Maydonovitch: analysis, collating and interpretation of the data, drafting of the manuscript. Roy K.H. Wong: interpretation of data and drafting of the manuscript. All authors approved the final version of the manuscript.

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