

Incidental Gastric Eosinophils in Patients With Eosinophilic Esophagitis: Do They Matter?

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ABSTRACT

Background and Aim: Some patients with eosinophilic esophagitis (EE) (>15 eosinophils/high-power field on esophageal mucosal biopsies and lack of response to acid suppression and/or normal pH probe study) demonstrate incidental eosinophilic inflammation of the gastric mucosa. It is unclear whether patients with EE and normal gastric biopsies (EE-N) are phenotypically different from patients with EE and gastric mucosal abnormalities (EE-A) (ie, >10 eos/hpf on gastric biopsies). The aim of the study was to compare the clinical features and response to therapy among patients with EE-N and EE-A.

Patients and Methods: Medical records of all of the EE-A and a random group of patients with EE-N diagnosed during an 8-year period were reviewed. A subgroup analysis of patients treated with swallowed fluticasone with a repeat esophagogastroduodenoscopy within 6 months of starting therapy was also performed.

Results: During the study period, 41 patients had EE-A. When compared to 50 random patients with EE-N, no clinical differences were noted, including sex, age, presenting symptoms, esophageal histology, and atopy history. Eleven (27%) of the 41 EE-A and 14 (28%) of the 50 EE-N patients were treated with swallowed fluticasone, and the response was similar among the groups. The mean esophageal eosinophils/high-power field among the EE-A group dropped from 47 to 8 compared with a 46 to 7 drop among the EE-N group treated with fluticasone therapy ($P=0.91$). In 9 (82%) of the 11 patients with EE-A treated with fluticasone, there was resolution (7 of 9) or significant improvement (2 of 9) of gastric eosinophilia.

Conclusions: Patients with EE-A and EE-N have similar clinical presentations. Incidental gastric inflammation does not predict a worse response of esophageal inflammation to fluticasone and should not exclude its use in patients with EE-A. In fact, gastric inflammation responded to swallowed fluticasone in the majority of patients with EE-A. This observation should foster further investigation into pathogenesis of EE and presumed esophagogastric inflammatory axis.

Key Words: eosinophilic esophagitis, eosinophilic esophagogastritis, eosinophilic gastritis, fluticasone, topical steroids

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Eosinophilic esophagitis (EE) is a clinicopathological entity characterized by eosinophilic infiltration of the esophageal epithelium (≥ 15 eosinophils/high-power field [eos/hpf] in 1 or more fields) in the absence of gastroesophageal reflux as evidenced by a normal pH monitoring study of the distal esophagus or lack of response to acid-suppressive therapy (1). It is the most common clinical entity of the eosinophilic gastrointestinal disorders (EGID) and is thought to be limited to the esophageal epithelium without significant eosinophilic inflammation of the remainder of the upper gastrointestinal (GI) tract mucosa. Although there is consensus that the healthy human esophagus is devoid of eosinophils, eosinophil concentration and spatial arrangements within the rest of the GI tract at baseline have not been agreed upon (2). Thus, definitive diagnostic criteria for eosinophilic inflammation of GI compartments other than the esophagus are lacking, although limited available data have shown normal eosinophil density in the stomach (antrum and fundus) of children to be <10 eos/hpf and in the duodenum to be <30 eos/hpf (3,4). On the basis of these, a subset of pediatric patients presenting with symptoms suggestive of EE are found on histopathology to have gastric eosinophilia in the absence of small bowel involvement. It is unclear whether these patients are phenotypically different from patients with solitary EE and whether their disease is merely an extension of the inflammation beyond the esophagus or a distinct disease entity.

Historically, eosinophilic gastritis has been considered a part of eosinophilic gastroenteritis (EG), an uncommon heterogeneous disorder characterized by eosinophilic infiltration in 1 or more areas of the GI tract, most commonly stomach and small intestine, in the absence of parasitic or extraintestinal disease (5). In general, patients with EG tend to have a wide range of presentations based on the anatomic location of the disease (stomach, duodenum, ileum) and depth of tissue involvement (mucosal, muscularis, serosal) (6,7). The predominant presenting symptoms can vary among vomiting, abdominal pain, diarrhea, weight loss, protein losing enteropathy, and ascites (7,8). There are also several reports of isolated eosinophilic gastritis presenting as nodular, concentric narrowing of the antrum producing outlet obstruction (9–11).

We have encountered a subset of patients, in our vast cohort of patients with EE, who have EE and what we considered incidental gastric eosinophilia with normal small bowel biopsies. The aim of this study was to compare the clinical features and response to therapy of patients with EE with and without incidental gastric eosinophilia.

PATIENTS AND METHODS

Patients

All of the patients between the ages of 1 and 18 years who underwent esophagogastroduodenoscopy (EGD) between 1999 and 2007 in the Division of Gastroenterology, Hepatology, and Nutrition at the James Whitcomb Riley Hospital for Children, Indiana University School of Medicine, Indianapolis, and demonstrated EE and gastric mucosal abnormalities (EE-A) (defined as ≥ 15 eos/hpf on

distal and/or mid-esophageal biopsy, with lack of response to acid-suppressive therapy and/or normal 24- to 48-hour intraesophageal pH-monitoring study, ≥ 10 eos/hpf on gastric biopsy, and histologically normal duodenal mucosal biopsies) were identified. A random group of patients with EE and normal gastric biopsies (EE-N) (defined as ≥ 15 eos/hpf on distal and/or mid-esophageal biopsy, with lack of response to acid-suppressive therapy and/or normal prolonged intraesophageal pH monitoring study, and histologically normal gastric and duodenal mucosal biopsies) selected based on a randomization table and diagnosed within the same period were included. Indications for EGD included abdominal pain, vomiting, dysphagia, and failure to gain weight. Medical records were reviewed for patient demographics, comorbid conditions, atopy history, allergy testing results, endoscopy findings, and histological data. Patients were excluded if they had coexistent *Helicobacter pylori* infection or any condition requiring immunosuppressive therapy such as inflammatory bowel disease and malignancy, or were status postorgan transplant. A subgroup analysis of patients in both groups treated exclusively with swallowed fluticasone with a repeat EGD within 6 months of starting therapy was also performed. The institutional review board of Indiana University/Purdue University, Indianapolis approved the study.

Endoscopy and Histology

Dictated EGD reports were reviewed in detail for presence of vertical lines/linear furrows, white specks/plaques, and erosions. Esophageal mucosal biopsies were obtained from the distal esophagus (ie, 3 cm proximal to the esophagogastric junction) in all of the patients and from the mid-esophagus (ie, 8 cm proximal to the esophagogastric junction) in most patients. Gastric biopsies were obtained from antrum and body. All of the specimens were oriented on a filter paper, formalin-fixed, paraffin-embedded, and hematoxylin and eosin stained. Pathology reports were reviewed for maximum number of eosinophils/high-power field at $\times 40$ magnification covering an area of 0.4 mm^2 . Basal cell hyperplasia (BCH) was documented.

Definition of Response

Patients treated with swallowed fluticasone were receiving exclusive topical therapy. The starting dose was 2 puffs of $110 \mu\text{g}$ per actuation for ages 1 to 10 years and $220 \mu\text{g}$ per actuation for ages 11 to 18 years 4 times a day with a nil per os status for 30 minutes post-administration. The medication was administered

for 4 weeks and then gradually weaned off during the following 8 weeks. Foods identified as possible allergens by radioallergoabsorbent tests were excluded from any patient's diet. Esophageal response to fluticasone therapy was defined as ≤ 5 eos/hpf on all of the esophageal biopsies obtained at repeat EGD. We defined gastric response as either complete resolution (ie, absence of eosinophils in gastric mucosal biopsies) or significant improvement (ie, $>50\%$ reduction in the number of eosinophils/high-power field on any of the repeat gastric mucosal biopsies).

Statistical Analysis

Primary analysis compared the EE-N and EE-A groups for differences in clinical features, and a subgroup analysis of patients among the 2 groups treated with swallowed fluticasone was used to assess response of esophageal histology. Two-sample *t* tests and χ^2 tests were used to analyze the data. Statistical significance was determined using an α level of 0.05 ($P < 0.05$).

RESULTS

Patients' Characteristics and Clinical Features

A total of 356 patients, aged between 1 and 18 years, were found to have ≥ 15 eos/hpf in mid- and/or distal esophageal biopsy during the study period. Of these, 41 (12%) patients met the study inclusion criteria of having concomitant eosinophilic gastritis on biopsy (EE-A). A male predominance (78%) was found in patients with EE-A, similar to the sex distribution of the 50 random patients with EE-N included in the study (72% men). Demographic characteristics and clinical features were similar between EE-A and EE-N groups (Table 1).

Endoscopic Features and Histological Response

Endoscopic appearance of the esophageal mucosa was similar between EE-A and EE-N groups with 95% and 90% of patients, respectively, manifesting vertical lines, white specks, and/or rings. Although all of the patients in the EE-N group and the majority (80%) of patients in the EE-A group had normal endoscopic appearance of the gastric mucosa, 8 patients with EE-A had either gastric mucosal erythema with or without edema (5/8) or erosions noted in the antrum (3/8). Distal esophageal biopsy results were available for all of the patients and were comparable between the EE-A and EE-N group with a mean eosinophils/high-power

TABLE 1. Patient demographics and clinical characteristics

	EE-A group N = 41	EE-N group N = 50	P
Mean age, y	6.9	7.2	NS*
Age range, y	1–17	1–17	NS
Men	32 (78%)	36 (72%)	NS
Presenting symptoms†			
Vomiting	22 (54%)	30 (60%)	NS
Abdominal pain	13 (32%)	15 (30%)	NS
Dysphagia	5 (12%)	9 (18%)	NS
Failure to thrive	3 (7%)	2 (4%)	NS
Clinical data‡			
Elevated serum immunoglobulin E level	6/12 (50%)	6/10 (60%)	NS
Peripheral blood eosinophilia§	19/25 (76%)	20/35 (57%)	NS
Positive food allergy skin testing	15/20 (75%)	21/34 (62%)	NS

EE-A = eosinophilic esophagitis patients with gastric mucosal abnormalities; EE-N = eosinophilic esophagitis patients with normal gastric biopsies. *NS = not significant ($P > 0.05$). †Patients may have >1 presenting symptom. ‡Not all patients had all of the studies performed, so numerators and denominators are reported. §Defined as >350 eosinophils/ mm^2 .

TABLE 2. Histological characteristics of esophageal biopsies

	EE-A (no. patients)	EE-N (no. patients)	P
Eosinophils/high-power field in distal esophagus mean $\pm$ SD (no. patients)	38.1 $\pm$ 19.6 (41)	40.02 $\pm$ 24.7 (50)	0.94
Eosinophils/high-power field in mid-esophagus mean $\pm$ SD (no. patients)	33.2 $\pm$ 19.7 (34)	36.7 $\pm$ 22.3 (40)	0.72

EE = eosinophilic esophagitis.

field of 38 (range 10–100) and 40 (range 6–120) and mean BCH of 76% and 71%, respectively (Table 2). The mean number of eosinophils/high-power field was 26 (range 10–100; median 20) in the gastric biopsies of the patients with EE-A and 0 in the EE-N group.

Swallowed fluticasone was prescribed for 11 of 41 (27%) patients with EE-A and 14 of 50 (28%) patients with EE-N. No differences were noted between the 2 treated groups in regards to demographics and clinical presentation. Response to swallowed fluticasone was similar among the groups. The mean esophageal eosinophils/high-power field in the EE-A group dropped from 47 to 8 versus a 46 to 7 drop in the EE-N group with fluticasone therapy ($P = 0.91$) (Table 3). Two of the 11 (18%) patients with EE-A and 4 of the 14 (29%) patients with EE-N had persistent esophageal eosinophilia (>5 eos/hpf). There were no differences in terms of clinical characteristics between responders and nonresponders.

In 9 of the 11 (82%) patients with EE-A treated with fluticasone, there was resolution ($N = 7$) or significant improvement ($N = 2$) of the gastric eosinophilia (Fig. 1). The 2 patients with the improved gastric eosinophilia had 100 and 42 eos/hpf at baseline and 22 and 18 eos/hpf at the subsequent EGD. In addition, they had complete resolution of their esophageal eosinophilia. As for the 2 of 11 patients with EE-A who had no improvement in gastric eosinophilia with fluticasone therapy, the gastric eosinophils/high-power field counts were 25 and 17 pretreatment and 30 and 15 at repeat EGD. The esophageal biopsies showed clearance of inflammation in 1 patient and no improvement in the other. Eight of these 11 patients with EE-A were asymptomatic at the time of their second endoscopy, whereas 3 remained symptomatic with abdominal pain. Interestingly, these 3 patients had normal repeat gastric biopsies.

DISCUSSION

During the last decade, EE has emerged from a rarely recognized entity into a frequently encountered condition in patients of all ages, presenting with a variety of gastrointestinal (GI) complaints including vomiting, abdominal pain, dysphagia, and failure to gain weight (1). Most often these patients demonstrate eosinophilic inflammation limited to the esophageal mucosal biopsies, although over the years we have encountered patients with EE who also have incidental eosinophilic inflammation on gastric biopsies in the absence of any small bowel involvement. The

clinical course of these patients is undefined in the literature to the best of our knowledge, prompting a review of our experience with this particular group of patients.

Although published consensus guidelines on EE consider a peak eosinophil count/high-power field >15 in esophageal mucosal biopsies to be diagnostic of EE, significant eosinophilic infiltration of the remaining GI tract is not widely agreed upon. This is due to the fact that there has been a paucity of investigations into the normal number and regional distribution of eosinophils in the pediatric GI tract. Lowichik and Weinberg (3) quantified, post-mortem, eosinophils in the mucosal layer of the GI tract in pediatric patients. Their detailed sampling revealed consistently low eosinophil density of <10 eos/hpf in the stomach. Debrosse et al (4) reported on 19 biopsies from 19 children undergoing endoscopy, most often for abdominal pain; they found a mean number of eosinophils/high-power field of 1.9 ± 1.3 in the lamina propria of the antrum, with a maximum of 8 eos/hpf. On the basis of these 2 studies and on a requirement for diagnosis of eosinophilic gastritis of >10 eos/hpf, 12% of our patients with EE had concomitant incidental eosinophilic gastritis, thereby classifying them as EE-A.

Our study examined the clinical characteristics of children with EE-A and their response to topical corticosteroid therapy, and compared these to a similar-sized cohort of EE-N children. Patients with EE-A were similar to our EE-N group in terms of demographics, presenting symptoms, atopy history, and response to therapy. We did not have a cohort of patients with EG to study, but the published literature would suggest that patients with EG are dissimilar to patients with EE-A; the peak incidence of EG presentation is the third to fifth decade of life, although it can be seen at any age, and unlike the patients with EE-A and EE-N in whom emesis is the predominant presenting symptom, abdominal pain is the classic primary complaint in patients with mucosal-type EG. Other unique presentations of EG include anemia, occult GI bleeding, and gastric protein loss (12–14). Our results and the published literature would suggest that patients with EE-A have a closer clinical resemblance to the EE-N than to the EG population.

Presently, topical, swallowed corticosteroids and dietary modifications are the most commonly prescribed therapies for EE. Studies have shown that swallowed fluticasone is successful in achieving histological and clinical improvement in patients with EE (15–18). There is lack of consensus on the optimal therapy for significant eosinophilic inflammation not due to parasitic or

TABLE 3. Effect of fluticasone (F) on esophageal histology

	EE-A pre-F (no. patients)	EE-A Post-F (no. patients)	EE-N Pre-F (no. patients)	EE-N Post-F (no. patients)	P
Eosinophils/high-power field in distal esophagus (mean $\pm$ SD)	46.8 $\pm$ 25.1 (11)	8.36 $\pm$ 23.9 (11)	45.8 $\pm$ 21.9 (14)	7.28 $\pm$ 12.1 (14)	0.91
Eosinophils/high-power field in mid-esophagus (mean $\pm$ SD)	41.5 $\pm$ 21.4 (8)	10.6 $\pm$ 26.2 (9)	33.7 $\pm$ 17.0 (13)	2.46 $\pm$ 5.74 (13)	0.87

EE = eosinophilic esophagitis.

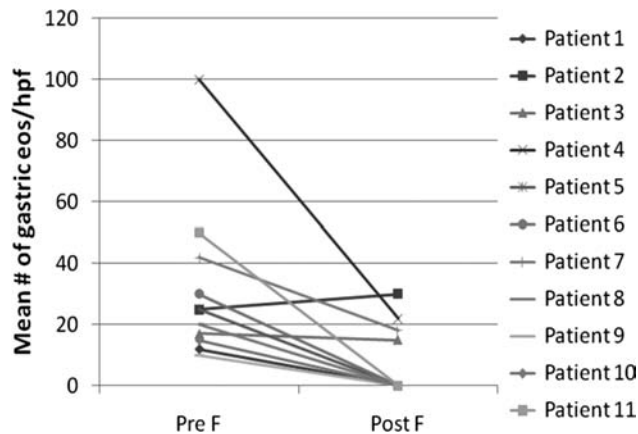


FIGURE 1. Response of gastric eosinophilia to fluticasone (F) therapy in eosinophilic esophagitis patients with gastric mucosal abnormalities.

extraintestinal disease in the remainder of the GI tract, but it seems that systemic steroid therapy remains the main therapy in patients in whom diet restriction is not feasible or has failed to improve the disease (7,9,19,20). Limited improvement with sodium cromoglycate has been reported (21,22), and there is a report of improvement with montelukast in patients with EG (23). The exact mechanism through which swallowed fluticasone exerts its effect on esophageal eosinophilia and the possibility of it clearing gastric eosinophilia is unknown. Nevertheless, we treated our patients with EE-A as we do EE-N children, and the response of the esophageal inflammation to swallowed fluticasone in our patients with EE-A was similar to that in the EE-N group. In fact, 82% of patients with EE-A and 71% of patients with EE-N treated with fluticasone had complete resolution of the esophageal eosinophilic inflammation. The presence of gastric inflammation did not alter the response of the esophageal inflammation to topical corticosteroid therapy, and having EE-A did not seem to predict a more aggressive phenotype of EE. Interestingly, eosinophilic gastric inflammation improved in 82% of patients with EE-A treated with swallowed fluticasone. We hypothesize that this improvement could be related to the residual effect of the swallowed fluticasone on the gastric antrum or, and more likely, the attenuation of the inflammatory axis that is responsible for both the esophageal and gastric inflammation through a systemic effect of the medication. Further studies, however, would be needed to solidify this hypothesis.

Our study, being retrospective, carries limitations. During the study period, our patients with EE were not treated according to a uniform standard protocol but rather with a variety of interventions including dietary modifications and systemic and topical corticosteroid therapy (18). Regardless, we were able to compare a dozen children with EE-A and EE-N who each had received only swallowed fluticasone therapy. Another potential limitation is the variable timing of follow-up endoscopy within 6 months of therapy initiation. We feel that this variability between endoscopies should not negatively affect our results because EE is considered a chronic condition (24).

CONCLUSIONS

In summary, our large cohort of EE-A children was clinically similar to a group of patients with EE-N. Presence of gastric inflammation was not predictive of an aggressive phenotype of EE. In fact, the gastritis responded to topical steroid therapy in the majority of patients with EE-A. Although these findings could be

incidental, they raise the possibility of an allergic esophagogastric inflammatory axis, which should foster mechanistic studies into the pathophysiology of EE. Prospective randomized controlled trials and natural history studies are needed to further examine the role of topical steroid therapy in the treatment of patients with EE-A and evaluate the natural course of their illness.

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