

Eosinophilic Gastrointestinal Disorders (EGID) with Peripheral Eosinophilia: A Retrospective Review at Mayo Clinic

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Abstract

Background and Aims Hypereosinophilic syndrome (HES) is defined by significant eosinophilia ($>1,500$ eos/ μ l), which often leads to end-organ damage/dysfunction. It is unclear if the presence of significant peripheral eosinophilia ($>1,500$ eos/ μ l) indicates a more aggressive form of eosinophilic gastrointestinal disorder (EGID).

Methods A database query of the Mayo Clinic Rochester electronic records (1995–2008) was performed using several search terms for eosinophilic gastrointestinal disease, and 161 records were reviewed. Patients under 18 years age, those without Mayo-reviewed pathology specimens, those with eosinophilic esophagitis only, and/or those with evidence of secondary etiologies for GI eosinophilia were excluded. A total of 39 were found to have primary EGID. We compared individuals with biopsy-proven primary

EGID based on whether they had significant peripheral eosinophilia ($\geq 1,500$ eos/ μ l) (group A) or not (group B).

Results Group A tended to have more atopy (A: 12/15; B: 11/24; $p = 0.03$) and more extensive segmental involvement of the GI tract ($p = 0.001$). None with available studies had evidence of cardiac (A: 7/15; B: 6/24) or bone marrow (A: 10/15; B: 6/24) involvement. The two thromboembolic events in group A after diagnosis did not translate to significantly greater risk (HR = infinity, $p = 0.13$; group A vs. B). Doses of initial (A: 40 mg/day; B: 55 mg/day; $p = 0.17$) and maintenance prednisone (A: 8.75 mg/day; B: 7.5 mg/day; $p > 0.90$) were similar. Group A was significantly more likely to need maintenance prednisone (77 vs. 8%, $p = 0.001$), with a median treatment duration of 52 weeks. Recurrence of symptoms (and peripheral eosinophilia) during prednisone taper was common in both groups. Prednisone-sparing agents (hydroxyurea, imatinib mesylate, interferon (IFN)- $\alpha 2b$, anti-interleukin (IL-5) monoclonal antibody) were more commonly used in group A (73 vs. 8%; $p < 0.0001$).

Conclusions EGID with peripheral eosinophilia $\geq 1,500/\mu$ l is associated with atopy, greater GI segmental involvement, and uncertain risk of thrombosis. The common use of long-term steroids and variable responsiveness to nonsteroidal agents, particularly in group A, underscores the need for targeted therapies.

Keywords Eosinophilic gastrointestinal disorders · Eosinophilic gastroenteritis · Eosinophilia

Abbreviations

EC	Eosinophilic colitis
EEn	Eosinophilic enteritis
EG	Eosinophilic gastritis
EGE	Eosinophilic gastroenteritis

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EGID	Eosinophilic gastrointestinal disorders
EoE	Eosinophilic esophagitis
HES	Hypereosinophilic syndrome
IFN	Interferon

Background and Aims

Eosinophilic gastrointestinal disorders (EGID) comprise a group of conditions characterized by inappropriate eosinophilic infiltration of the bowel wall, and distinction is made between primary and secondary forms. This study focuses on primary EGID, which are limited to disease in the absence of identifiable secondary causes of GI eosinophilia, including drug reactions, parasitic infections, inflammatory bowel disease, and malignancy [1]. Eosinophilic infiltration can occur in one or more gastrointestinal segments. Eosinophilic esophagitis (EoE), eosinophilic gastritis (EG), eosinophilic gastroenteritis (EGE), eosinophilic enteritis (EEn), and eosinophilic colitis (EC) refer to abnormal eosinophilic inflammation in the esophagus, stomach, stomach and small bowel, small bowel, and colon, respectively. Aside from reference to the involved segment, EGID are subcategorized on the basis of the level of histologic involvement: mucosal, muscularis, and serosal forms [2]. Histological discrimination is useful as the symptomatology of disease varies according to the depth and extent of eosinophilic infiltration [3].

The diagnoses of EGID are guided by both a consistent clinical presentation and dense eosinophil infiltration on gastrointestinal biopsy or resection. Uniform diagnostic guidelines have yet to be established. The challenge is that eosinophils are normally found in varying quantities in healthy mucosa beyond the esophagus [4]. However, there have been proposed cut-offs, such as 25 eos/high power field (HPF) [5]. As a diagnosis of exclusion, the evaluation of the patient begins with assessment for more common conditions like parasitic infection, inflammatory bowel disease, drug reaction, and functional bowel disorders [6]. Therefore, the diagnosis may be delayed by years, decades, or even completely missed [5].

Mild peripheral eosinophilia has been noted in about two-thirds of individuals with eosinophilic gastroenteritis [7]. However, significant eosinophilia (defined as $\geq 1,500$ eos/ μ l) is less common. The 2010 working definition of hypereosinophilic syndrome (HES) proposes: (1) eosinophilia $\geq 1,500$ eos/ μ l on at least two occasions or evidence of prominent and symptomatic tissue eosinophilia; and (2) exclusion of secondary causes of eosinophilia [8]. The 6-month duration of eosinophilia as set forth by Chusid has become obsolete [9]. Under the 2010 criteria, EGID with significant eosinophilia falls under

“overlap variant of HES,” which is characterized by persistent peripheral and tissue eosinophilia restricted to specific organs (e.g., the GI tract) [8].

Based on observational literature, primary EGID is generally considered a benign condition [4]. In contrast, HES is often a multi-system disorder associated with greater morbidity and mortality. EGID accompanied by significant peripheral eosinophilia is considered an overlap variant of HES in the expanded definition set forth in 2006 [10], and more recently in 2010 [8]. We evaluated individuals with biopsy-proven EGID with peripheral eosinophilia ($\geq 1,500$ eos/ μ l) and without peripheral eosinophilia ($< 1,500$ eos/ μ l). The clinically important question is whether we can distinguish individuals with EGID with a more progressive course who need aggressive therapy to prevent tissue remodeling and fibrosis associated with HES from those with a milder course who can be treated on the basis of symptoms. In this review, we evaluate if significant peripheral eosinophilia is a marker of more aggressive disease.

Methods

This is an IRB approved, retrospective case review of 39 individuals with biopsy-proven EGID. They were identified through a search of Mayo Clinic Rochester patient records dating back to 1995 by the Division of Biomedical Statistics and Informatics, using the following diagnostic terms: EoE, EG, EGE, EEn, and EC. Author JL examined the records of patients meeting the following criteria: (1) 18–65 years old at time of diagnosis; (2) documentation of a clearly “positive” biopsy of the distal gastrointestinal tract (beyond esophagus); (3) negative workup for secondary causes of eosinophilia. Patients with sole EoE were excluded because presentation and management of EoE are different from that of the more distal EGIDs. On each available biopsy, the number of eosinophils was evaluated as in lamina propria and intraepithelial per high power field by one experienced gastrointestinal pathologist (TW). Several individuals had numerous slides for a particular segment of the GI tract. All counts were obtained and the highest count was used for statistical analyses.

Symptoms of dysphagia, abdominal pain/cramping, early satiety/bloating, nausea, vomiting, and loose stools were quantified with a binary scoring system of 1 for presence, and 0 for absence of each symptom (maximum score 6). When available and appropriate, indirect values of peripheral eosinophilia were converted into a direct absolute eosinophil count (AEC) by virtue of unit conversion (i.e., from liter to microliter). An eosinophil count of 1,500 or greater was used as the cut-off value for defining significant eosinophilia (i.e., group A). This cut-off value was

chosen because this is conventionally used as the threshold for further evaluation for underlying marrow-derived clonal abnormalities [11].

Treatment histories were reviewed. Since most underwent trials of prednisone, responses were graded in three different categories: (1) No improvement; (2) Response with immediate relapse (e.g., symptoms and/or eosinophilia rebounding *within* 1 month (often in a matter of days) after completing prednisone taper); (3) Response with delayed relapse (rebound of symptoms and/or eosinophilia *after* 1 month after stopping prednisone).

Statistical Analysis

Wilcoxon rank-sum tests were used to compare continuous variables between the groups. Pearson's Chi-square tests or Fisher's exact tests, as appropriate, were used for group comparisons of nominal categorical variables, while the Cochran–Mantel–Haenszel row means score test was used for ordinal categorical variables (e.g., total symptom score and number of GI segments involved). A Cox proportional hazards model was used to compare the groups for adverse events (thrombotic events) post-diagnosis.

Results

The above-mentioned search yielded records of 161 patients (refer to Fig. 1 for reasons for exclusion). The remaining 39 individuals were categorized into two groups on the basis of presence [group A: median 3,268 eos/ μ L (range 1,510–13,000)] or absence [group B: median 670 eos/ μ L (range 0–1,440)] of significant peripheral eosinophilia at initial evaluation. The demographic variables of the two groups were comparable (Table 1). There was more atopy in group A [80% as compared to 46% in group B ($p = 0.03$)] and a tendency towards higher serum IgE ($p = 0.09$). Positivity on skin testing to foods and aeroallergens was very common in both groups ($p > 0.90$). Interestingly, the breadth of symptoms at presentation between the two groups, as quantified by symptom scores, was comparable ($p = 0.25$).

Biopsies were reviewed by TW based on availability from 29 individuals (11 individuals from group A, 18 individuals from group B). Slides from the other ten individuals were unavailable ($n = 9$; from outside institutions formally read previously at Mayo) or unfit ($n = 1$; faded H&E stain) for review. Gastric (24/29; 83%) and small bowel (26/29; 90%) sampling was more common than the esophagus or colon (both 9/29; 31%). Individuals in group A tended to have a greater extent of biopsy-proven involvement of the gastrointestinal tract ($p = 0.001$), with at least two-segment involvement of the GI tract (100%).

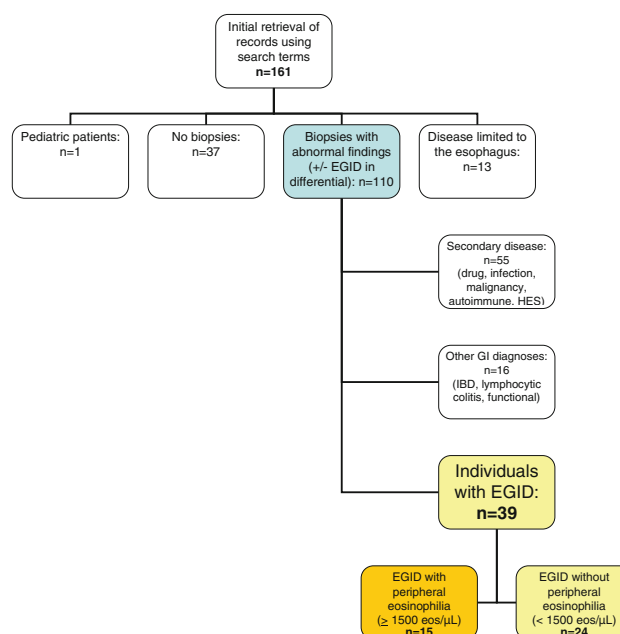


Fig. 1 Serial exclusion of initial pool of 161 individuals carrying at least one of the search term diagnoses (see “Methods”) in their electronic medical records at Mayo Clinic Rochester between 1995 and 2008

Those without peripheral eosinophilia (group B) had mostly one-segment involvement (67%). However, the density of tissue eosinophilia as quantified from available biopsies was similar in both groups (Table 2).

Two individuals from group A had thrombotic events (PE and stroke) at 20 months and 134 months out from initial EGID diagnosis, respectively, but this did not translate to a significant difference in the risk of thrombotic events post-diagnosis (HR = infinity, $p = 0.13$; group A vs. B). The individual's eosinophil count was normal when the pulmonary emboli were detected. Investigation did not reveal deep venous thrombosis, occult malignancy, or a hypercoagulable state. With regards to the stroke, the individual's eosinophil count at the time of the event is unknown, but records indicate that it was elevated 4 weeks prior to the event (at 2,000 eos/ μ L) as well as 3 weeks following the event (at 3,090 eos/ μ L).

Treatment data is summarized in Tables 3 and 4.

Prednisone

Prednisone use (initial dose, maintenance dose, therapeutic response recorded in the medical record) was documented in detail in over 50% of the 39 individuals (13 in group A, 12 in group B). The others pursued treatment elsewhere or did not undergo treatment with prednisone. Response rates were high in both groups (A: 13/13 = 100%; B: 9/11 = 82%). In those with available details, the prednisone response distribution (no improvement vs. response

Table 1 Clinical characteristics of individuals with EGID with high (group A) and normal eosinophil counts (group B)

	High eos (<i>n</i> = 15)	Normal eos (<i>n</i> = 24)	<i>p</i> value
Peripheral eosinophil count (eos/ μ l), median (range)	3,268 (1,510, 1,300)	670 (0, 1,440)	NR
Age of symptom onset (years), median (range)	33 (10, 54)	34 (15, 62)	0.65
Age at diagnosis (years), median (range)	39 (18, 55)	38 (18, 65)	0.91
Males, <i>n</i> (%)	8 (53%)	10 (42%)	0.48
Atopic history (allergic rhinitis, asthma, atopic dermatitis, food allergies documented in medical records), <i>n</i> (%)	12 (80%)	11 (46%)	0.03
Number of common symptoms (abdominal pain, bloating, nausea, vomiting, loose stools), <i>n</i> (%)			0.25
1	1 (7%)	4 (17%)	
2	2 (13%)	4 (17%)	
3	5 (33%)	5 (21%)	
4	3 (20%)	7 (29%)	
5	1 (7%)	4 (17%)	
6	3 (20%)	0 (0%)	
Serum IgE [kU/l], median (range) ^a	163 (20, 4,583)	86.9 (8, 2,327)	0.09
Positive food skin test, <i>n</i> (%) ^a	12 (92%)	8 (100%)	>0.90
Positive aeroallergens skin test, <i>n</i> (%) ^a	7 (88%)	6 (100%)	>0.90
Normal bone marrow evaluation (including normal cytogenetics), <i>n</i> (%) ^a	10 (100%)	6 (100%)	NR
Normal transthoracic ECHO, <i>n</i> (%) ^a	7 (100%)	6 (100%)	NR

^a Missing values exist**Table 2** Tissue eosinophilia and segmental involvement in the two groups

	High eos (<i>n</i> = 10)	Normal eos (<i>n</i> = 18)	<i>p</i> value
Number of involved GI segments, <i>n</i> (%) ^a			0.001
1	0	12 (67%)	
2	5 (50%)	4 (22%)	
3	5 (50%)	2 (11%)	
Tissue eosinophilia, median eosinophils/hpf (range) ^a			
Esophagus IE	>100 (7, >100)	55 (0, >100)	0.18
Gastric IE	7 (0, 25)	6.5 (0, 50)	0.81
Gastric LP	>100 (3, >100)	>100 (0, >100)	0.17
Small bowel IE	0 (0, 10)	1 (0, 11)	0.47
Small bowel LP	40 (17, >100)	33 (13, >100)	0.94
Colon IE	0 (NR)	0 (0, 25)	0.37
Colon LP	90 (NR)	10.5 (5, >100)	0.23

IE intraepithelial, LP lamina propria

^a Missing values exist

with immediate relapse vs. response with delayed relapse) was similar in the two groups ($p = 0.89$). However, those with EGID associated with hypereosinophilia were more likely ($p = 0.001$) to be on long-term maintenance prednisone at a median dose of 8.75 mg/day for a median duration of 52 weeks (see Table 3 for details).

Prednisone-sparing agents included cromolyn sodium, montelukast, hydroxyurea, IFN- α , imatinib mesylate, azathioprine, and anti-IL5 (Mepolizumab[®]; compassionate release, GlaxoSmithKline). The use of more potent agents (the latter five) was more common in group A (73 vs. 8%, $p < 0.0001$; see Table 4 for details). Among individuals in group A, hydroxyurea ($n = 1$), imatinib mesylate ($n = 1$),

and IFN- α 2b ($n = 4$) allowed for prednisone to be tapered down to 5 mg per day or less.

Montelukast

Montelukast was tried in two individuals from group A and two individuals from group B. One of the two patients from group A relied on this and avoidance of foods to which he tested positive. The other also had symptomatic relief from montelukast along with cromolyn, but due to persistent hypereosinophilia, relied on periodic courses of elemental diet to suppress eosinophilia, and underwent trials of various immunomodulating agents, eventually ending up on

Table 3 Prednisone treatment profiles of individuals with EGID with high and normal eosinophil counts

	High eos (<i>n</i> = 13)	Normal eos (<i>n</i> = 12)	<i>p</i> value
Initial prednisone dose (mg/day), median (range)	40 (20, 60)	55 (20, 100)	0.17
Duration (weeks), median (range)	8 (1, 52)	7 (1.3, 32)	0.97
Number (%) of patients on maintenance therapy	10 (77%)	1 (8%)	0.001
Maintenance prednisone dose (mg/day), median (range)	8.75 (2, 10)	7.5 (7.5, 7.5)	>0.90
Duration (weeks), median (range)	52 (8, 144)	12 (12, 12)	0.29

anti-IL5 (Mepolizumab®). Sustained clinical remission (up to 4.2 years, last documented in 2003) was achieved in one individual from group B.

Azathioprine

One individual from group B had good control on a regimen of Azathioprine 100 mg/day with cromolyn taken four times daily.

Hydroxyurea

Hydroxyurea at 500 mg and prednisone at 5 mg helped one patient to achieve disease remission. Three months later, hydroxyurea had to be increased to 1,000 mg/day due to increasing symptoms and eosinophilia.

Imatinib Mesylate

One individual achieved symptom and eosinophilia control with imatinib mesylate at 100 mg per day, with prednisone 5 mg every other day.

Interferon

Five patients (four from group A, one from group B) underwent trials of IFN- α 2b at 3 million units three times a week. Duration of treatment was variable, ranging from 3 months to 3 years. It is possible that duration is longer; one patient from group A was followed for 2 years at Mayo Clinic Rochester, but then transitioned to management with the home provider. One individual was eventually transitioned to weekly pegylated interferon due to signs of refractory disease after being on IFN- α 2b for 3 months. Her last documented visit in 2001 indicated that her eosinophil counts were trending up and the pegylated interferon was held, with a designated date for re-initiation.

Anti-IL-5 Monoclonal Antibody

Mepolizumab® (compassionate release, GlaxoSmithKline) alleviated symptoms and eosinophilia in two patients, but had to be discontinued in one due to a stroke event that was

diagnosed after she had received two doses of the medication. The other individual continues on this medication in remission as of most recent records in June of 2010.

Anti-IgE Monoclonal Antibody

There was one individual who received this medication monthly through an open-label trial. This was not continued due to dramatic rebound of eosinophilia followed by symptoms several weeks after trial completion.

Discussion

This study characterized the clinical features and treatment profiles of individuals with biopsy-proven primary EGID with and without peripheral eosinophilia evaluated at a large tertiary referral center. All 39 individuals presented to the gastroenterology clinic. We observed that individuals with EGID accompanied by significant peripheral eosinophilia were more likely to have atopic histories. Most, but not all, were evaluated by an allergist-immunologist (A: 71%; B: 63%).

Concomitant allergic disorders, present in 59% of our 39 patients, have been reported to be highly prevalent in patients with EGID [12]. One Web-based pediatric registry of 57 EG patients revealed that 80% had a coexisting atopic disorder and 62% had evidence of food sensitization [13]. The literature cites figures ranging from 25–80% of individuals with an EGID as being atopic [11, 14]. Our data support this association.

It is recommended that EGID patients with peripheral eosinophilia exceeding 1,500/ μ l receive timely management targeting eosinophilia reduction due to the risk of end-organ damage and thromboembolic disease [11]. The recommended diagnostic evaluation of EGID includes a thorough evaluation for secondary etiologies for gastrointestinal eosinophilia (i.e., parasitic disease, malignancy, inflammatory bowel disease, drug reactions). A referral to Allergy & Immunology is appropriate for evaluation of concomitant atopic conditions and food allergies with diagnostic skin prick and serum antigen-specific IgE (RAST) testing, which may guide food elimination/avoidance strategies. A bone

Table 4 Treatment profiles of individuals with EGID with high (group A) and normal (group B) eosinophil count

(Shaded gray block indicates history of use; * Symptom response (and peripheral eosinophil reduction)

Prednisone column: X = documentation of prior prednisone use history without dose/duration and clear evidence of response status

	Prednisone (20-100mg daily; initial dose)	Elemental diet (Vivonex)	Budesonide (3mg qHS to QID)	Cromolyn (100-200 mg QID)	Montelukast (10 mg/d)	Azathioprine (100 mg/d)	Hydroxyurea (500-1000 mg/d)	Imatinib mesylate (100-200 mg/d)	IFN- α 2b (3 million units 3 days/wk)	Pegylated IFN (40 mcg/wk)	Anti- IL5	Anti- IgE
A1	*				*							
A2	*			*	*							
A3	*	*									*	
A4	*											
A5	*											
A6												
A7	*		*								*	
A8	*	*							*			
A9	*	*						*				
A10	*	*										
A11												
A12	*						*					
A13	*											
A14	*											
A15	*											
B1												
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B8	*				*	*						
B9												
B10	*											
B11	*											
B12	X											
B13												
B14	X											
B15												
B16	*											
B17	X											
B18	*											
B19	X								*			
B20				*								
B21	*											
B22	*											
B23	X											
B24	*		*									

marrow biopsy and echocardiogram are also necessary components of the hypereosinophilia workup. Our data would bring these recommendations into question. Our individuals with EGID and significant eosinophilia had more extensive GI tract involvement. None of the individuals in our group A with bone marrow biopsies ($n = 10$ of 15) or echocardiograms ($n = 7$ of 15) had evidence of malignant disease in the marrow or involvement of the heart. Although our data indicate that peripheral eosinophilia is not associated with a greater risk for developing thromboembolic events, we would not dismiss this observation given the small sample sizes and variable duration of follow-up.

Treatment data were not available for all 39 individuals. However, the conclusions drawn from analysis are in keeping with what has been published on EGID as being a prednisone-responsive condition. Duration of the prednisone courses with or without tapers varied widely among individuals under each group. The more prolonged courses given for patients in group A were often justified by efforts to decrease eosinophilia as well as symptoms.

To date, there are no FDA-approved medications to specifically treat any of the EGID [15]. The current mainstay of management for patients with EGID is corticosteroids, which have been shown to inhibit eosinophil growth factors IL-3, IL-5, and GM-CSF [5]. Estimates ranging from 70–90% of prednisone responsiveness have been cited in the literature. However, given the waxing and waning clinical course of this spectrum of disease, it is common for individuals with EGID to be placed on long-term corticosteroid therapy. Only one patient (from group B) had disease that was significantly managed with intermittent prednisone, requiring only two to three 1-week courses of prednisone 40 mg/day in a year. Recurrence of symptoms and/or rising peripheral eosinophil counts was common in both groups.

Alternative agents are needed to minimize the significant adverse effects of long-term steroids, which include fluid and electrolyte imbalances, hyperglycemia, growth suppression, bone demineralization, endocrinopathies, and posterior subcapsular cataracts. Dietary strategies, such as elimination and elemental diets, have been shown to improve clinical symptoms and reduce mucosal eosinophils, primarily for EoE [16]. Restrictive diets may be difficult to adhere to, but remain a nontoxic option for a condition that is known to wax and wane. Response to an elemental diet has been explained by decreasing the inflammatory response to dietary antigen, as children with EoE have been found to have increased intestinal permeability [17]. Although it is well accepted that an elemental diet is a costly and unsustainable option for longer-term management, it does offer patients a steroid-sparing approach to flares.

Second-line agents used for EGID, especially those considered to have overlap HES and/or have steroid-refractory disease, include subcutaneous IFN- α , which has been noted to have a 1–2 week onset of action. Another option is anti-IL-5 monoclonal antibody (Mepolizumab[®], compassionate release from GlaxoSmithKline), which has been shown to significantly reduce tissue eosinophilia [18, 19]. However, it can be associated with rebound eosinophilia once discontinued [20, 21]. Imatinib mesylate is a tyrosine kinase inhibitor that serves as first-line therapy for hypereosinophilic syndrome (HES) with myeloproliferative features (c-kit deletion), but is generally considered a last-line option for refractory EGID [22]. One case report documented success of this agent, sustained at a dose of 200 mg daily, in five patients with hypereosinophilia and normal IL-5 levels [23].

The use of steroid-sparing agents was more common in group A and helpful in cases of steroid-refractory symptoms and/or eosinophilia. Individuals with EGID with peripheral eosinophilia should be evaluated by an allergist-immunologist and/or a hematologist for guidance on treatment with these potent agents.

There are several limitations to this study. Due to its retrospective nature, not all individuals had diagnostic allergic testing, echocardiograms, and bone marrow biopsies. Biopsies were not taken systematically from esophagus to colon. In addition, several were performed at different institutions (two from group A, six from group B) and could not be read due to faded staining (one from group A). For these individuals, there was medical documentation in the EMR regarding outside interpretations to justify inclusion into the study. However, our conclusion about the extent of GI involvement was based on prospective review and quantification of eosinophils from available specimen. Secondly, many of the patients initially evaluated at our medical center or presenting with request for a second opinion eventually sought local care. Hence, much of the follow-up was from a distance (e.g., subjective assessments and gleaned from updates from local providers) and specific dosing and taper schedules were not explicit.

In summary, we have presented our significant experience with patients who have EGID and were diagnosed and treated at our medical center between 1995 and 2008. We differentiated EGID with respect to the presence of peripheral eosinophilia ($AEC \geq 1,500$ cells/ μ l), and asked whether peripheral eosinophilia is a marker of more aggressive disease. Atopy and greater GI segmental involvement appears to be more common in the former group. Furthermore, two of these individuals also had thromboembolic events (multiple pulmonary emboli and embolic stroke). However, none of our patients with significant eosinophilia had evidence of cardiovascular or

bone marrow involvement. Certainly, we acknowledge the limitations of this study given its retrospective nature. However, our results do not significantly dispute what has been previously established, but it does provide additional clinical insight. Not surprisingly, longer courses of maintenance prednisone and utilization of more potent immunosuppressive prednisone-sparing agents were more common among those with EGID with peripheral eosinophilia. This highlights the need for further study of patients with hypereosinophilia and EGID.

Conflict of interest Ross Dierkhising, Joohee Lee, Catherine Weiler, and Tsung-Teh Wu have nothing to disclose in relation to this study. Jeffrey Alexander has consulting relations with Meritage Pharmacia and research funding from Merck and Novartis.

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