

Eosinophilic Gastroenteritis: An Underdiagnosed Condition

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Abstract

Background Eosinophilic gastroenteritis (EOGE) is a rare idiopathic disease characterized by eosinophil-predominant inflammation of the stomach and/or intestines. Our aims are to determine the epidemiology, clinical features and outcomes of EOGE cases in a tertiary-care hospital.

Methods Retrospective cohort study of patients with gastrointestinal eosinophilic infiltration from 2004 through 2014. All relevant specimens were reviewed by an expert pathologist. Significant eosinophilic infiltrate was defined as >25 eosinophils/HPF in the stomach or small intestine and >50 eosinophils/HPF in the colon.

Results Three hundred and sixty-one charts were reviewed and 13 EOGE cases were identified, including nine adults and four pediatric cases. The majority (78 %) of adult cases were females. Clinical presentation was variable; most patients (62 %) had abdominal pain, followed by diarrhea (31 %) and nausea/vomiting (31 %). Atopy and food allergies were present in 54 and 38 % of patients, respectively. Weight loss and failure to thrive were present only in pediatric cases (50 vs 0 %; $P = .01$). Most EOGE cases

(69 %) had peripheral eosinophilia, which was more prominent in patients with ascites compared to patients without ascites (37.3 ± 25.4 vs 9.3 ± 5.4 %; $P = .01$). Among patients who had long-term follow-up; 30 % had spontaneous remission, 60 % responded to steroids and/or restriction diet, and 10 % had refractory disease.

Conclusion EOGE is an underdiagnosed condition. In contrast to eosinophilic esophagitis; the disease might be female-predominant in adults. High index of clinical suspicion is required for diagnosis. Further studies about the long-term outcomes and the efficacy of restriction diet in adult patients are required.

Keywords Eosinophilic gastroenteritis · Eosinophilic colitis · Eosinophilic esophagitis · Eosinophilic enteritis

Introduction

Eosinophilic gastroenteritis (EOGE) is an idiopathic disease that can affect one or more organs in the gastrointestinal (GI) tract including the stomach, small intestine and less commonly the colon [1]. EOGE is rare; 280 cases have been reported between 1937 and 2006 [2, 3], and over the last 10 years few additional small case series [4, 5] and many individual case reports of EOGE have been published [6]. EOGE causes patchy inflammation with various depth of eosinophilic infiltration in the involved organ(s). The Klein classification [7] divides EOGE into mucosal, muscular, serosal and pan-mural disease, based on the involved layer(s). The disease affects both males and females with a slight male predominance in adults [2]. All age groups can be affected and the incidence peaks in the third to fifth decades of life [8]. Personal history or family history of atopic diseases like asthma, hay fever or eczema

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is present in more than 70 % of cases [9]. In addition, food allergies are commonly seen in EOE patients [10].

Clinical presentation is widely variable. Patients with predominant mucosal disease typically present with nausea, vomiting, diarrhea, iron deficiency anemia, malnutrition, protein-losing enteropathy and weight loss, and the last two are more common in pediatric patients [10, 11]. Muscular disease can be associated with intestinal obstruction (mainly jejunal obstruction), and serosal disease is associated with bloating, ascites and possibly a better response to corticosteroid therapy [12].

EOE is a diagnosis of exclusion [9, 13]. The diagnosis requires a combination of non-specific gastrointestinal (GI) symptoms and eosinophilic infiltration of one or more organs including the stomach, small intestine and colon. Secondary causes of eosinophilic infiltration should be excluded [8]. Important secondary causes of eosinophilic infiltration and eosinophilia include parasitic infection, drug-induced eosinophilia, inflammatory bowel disease, hypereosinophilic syndrome and eosinophilic leukemia, malignant lymphoma, connective tissue disease and celiac disease [1, 6, 9]. Eosinophils are not present normally in the esophageal mucosa, and the presence of more than 15 eosinophils per high-power field (HPF) on light microscopy is diagnostic of eosinophilic esophagitis in the appropriate clinical setting [14]. However, variable number of eosinophils is present in normal conditions in the stomach, small intestine and colon. Many experts consider 20–25 eosinophils/HPF a cutoff for normal eosinophil count in the stomach and small bowel [15, 16]. The number is higher in pediatric patients; a study by DeBrosse et al. [17] showed that up to 26 eosinophils/HPF in duodenum and 50 eosinophils/HPF in colon are considered normal. Recent studies have shown slightly increased eosinophils in small intestinal and gastric biopsies obtained from patients with functional dyspepsia compared to healthy controls. The mean number of eosinophils in these studies is 20–25 eosinophils/HPF [18, 19]. However, when compared to EOE, functional dyspepsia is a distinct disease condition and has a different clinical course in our opinion. Peripheral eosinophilia is present in most EOE cases but is not required for diagnosis [2, 13, 20].

Endoscopic findings are variable and include mucosal erythema, edema, nodular appearance and occasionally ulcerated mucosal surfaces [12, 21]. Approximately half of the patients have normal-appearing mucosa endoscopically [4]. Patchy disease is not uncommon; multiple biopsies are recommended even with normal endoscopic exam [12]. The pathophysiology of EOE is not fully understood, and is thought to be a combination of IgE-mediated and non-IgE-mediated mechanisms; through highly differentiated Th2 cells [22]. After initial activation, eosinophils produce several cytokines including interleukin 3 (IL-3), interleukin 5 (IL-5) and granulocyte–macrophage colony-stimulating factor (GM-CSF) [23].

Corticosteroids are effective in 80–100 % of cases [24, 25], although there are no randomized controlled trials for EOE treatment, second-line therapeutic options are described in several cohort studies and case reports, such as mast cell stabilizers (sodium cromoglycate), antihistamines, leukotriene antagonists (montelukast), restriction diet, elemental diet, immunotherapy (desensitization), immunomodulators (azathioprine and 6-mercaptopurine), mepolizumab (IL-5 antibody), tumor necrosis factor inhibitors (e.g., infliximab) and IgE monoclonal antibody (omalizumab) [13, 21, 26–28]. Given the limited number of reported EOE cases, more data are required about the epidemiology, histologic features, clinical characteristics and outcomes of EOE.

Methods

We performed a retrospective cohort study at the University of New Mexico Hospital; a tertiary 580-bed teaching facility serving a population of 900,000 in Bernalillo County, New Mexico. The study was approved by the Human Research Protection Office (HRPO) and the Institutional Review Board at the University of New Mexico in November 2014 (study HRRC # 13-608).

Patient Selection

Chart review was performed on all cases that had a pathology report including the terms eosinophilic gastritis, eosinophilic enteritis, eosinophilic gastroenteritis or eosinophilic colitis. The cases included both endoscopic and surgical specimens submitted to the Pathology Department in the time period between January 2004 and December 2014. Cases that had increased eosinophils in gastric, small intestinal or colonic specimens were included, and a more detailed chart review was done, looking at the relevant clinical and procedural/surgical notes, laboratory and imaging results. In addition, the pathology slides for the included cases were examined by an expert GI pathologist.

Histology

After exclusion of non-relevant cases, an expert GI pathologist examined the pathology slides for all included cases. All tissue samples (mucosal biopsies and resection specimens) were scanned at low power to identify the area harboring the highest density of eosinophils. Eosinophils were then enumerated in a single HPF (400×) in the area of highest density for each patient sample. The presence or absence of infectious organisms (i.e., fungus and parasites), pill fragments, eosinophilic cryptitis, eosinophilic crypt abscesses, concurrent acute inflammation, and concurrent features of inflammatory bowel disease (chronic active colitis/ileitis) were also noted.

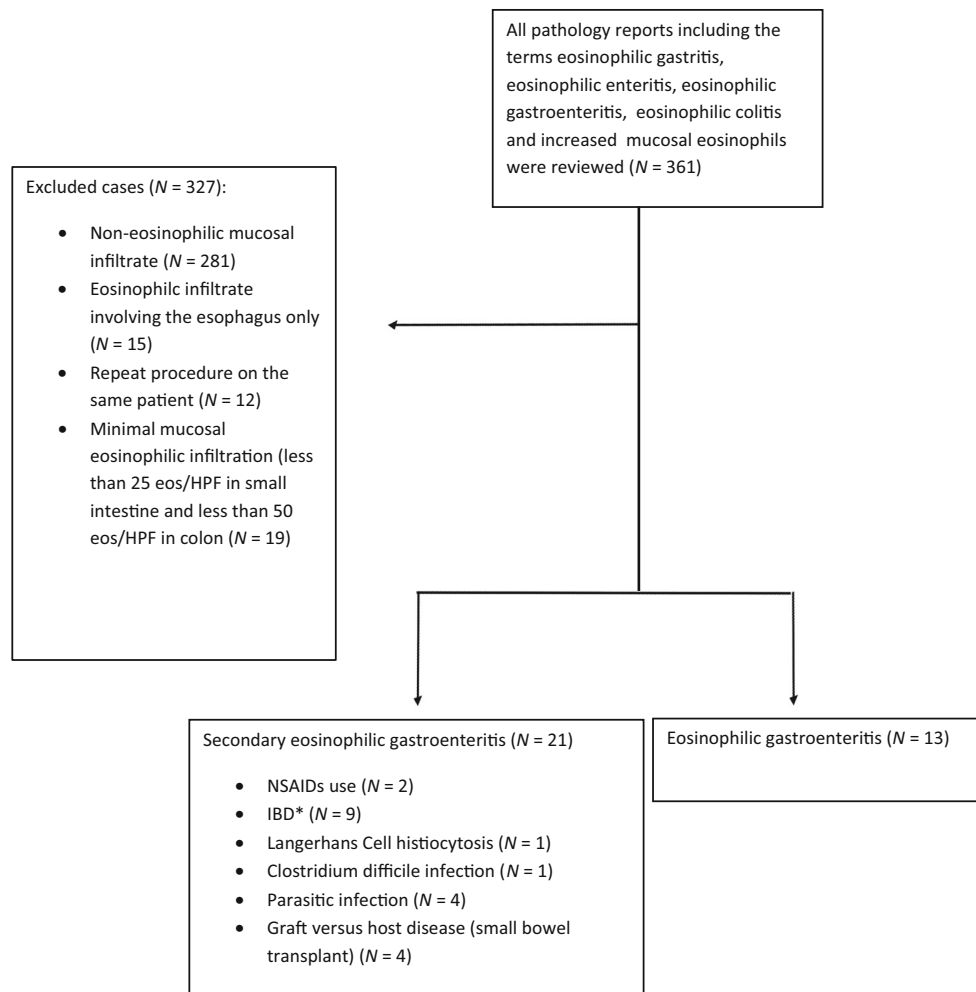


Fig. 1 Flow chart demonstrating the selection process of patients diagnosed with eosinophilic gastroenteritis.*IBD inflammatory bowel disease

Eosinophil distribution was described in specimens demonstrating submucosal tissue or deeper. The pathologist was blinded to all demographic and clinical data while recording his observations.

Statistical Analysis

For categorical variables, the number (N) and proportion (%) of cases were reported, and for continuous variables the mean values $\pm$ standard deviation (SD) were included. The comparison between two groups was performed using the Mann–Whitney test. A significant difference was defined as $P < .05$.

Results

Patients

We reviewed pathology reports including the terms eosinophilic gastritis, eosinophilic enteritis, eosinophilic gas-

troenteritis or eosinophilic colitis. Records of 361 subjects were reviewed; of these 327 subjects were excluded, due to the presence of non-eosinophilic mucosal infiltrate (N = 281), Eosinophilic infiltrate involving the esophagus only (N = 15), repeat procedure on the same patient (N = 12) and minimal eosinophilic infiltrate (less than 25 eosinophils per high-power field (HPF) in the stomach/small intestine or less than 50 eosinophils per HPF in the colon) (N = 19) (Fig. 1). Thirty-four cases had elevated eosinophils in gastric and/or small intestinal and/or colonic endoscopic biopsies or surgical resection specimens; of these, 21 cases were excluded due to the presence of secondary causes of increased tissue eosinophils. Thirteen cases had the diagnoses of eosinophilic gastroenteritis (EOGE) (Fig. 1). Of the 13 patients with EOGE, nine patients were adults (69 %) and five were men (38 %). The mean age in adults was 42.56 ± 6.26 , and in pediatric patients was 5.88 ± 3.38 years. The patient ethnicities were diverse and included seven Whites (54 %), four Hispanics (31 %), one Native American (7.8 %) and one Asian (7.8 %) (Table 1).

Table 1 Demographic and clinical characteristics of subjects with eosinophilic gastroenteritis

Total number of patients	13
Age at diagnosis (mean $\pm$ SD)	
Adult patients	42.56 $\pm$ 6.26
Pediatric patients	5.88 $\pm$ 3.38
Adult, ≥ 18 [N (%)]	9 (69)
Male	5 (38)
Race	
White	7 (54)
Hispanic	4 (31)
Native American	1 (7.8)
Asian	1 (7.8)
Clinical presentation [N (%)]	
Abdominal pain	8 (62)
Diarrhea	4 (31)
Nausea and vomiting	4 (31)
Hematemesis	1 (7.8)
Microcytic anemia	2 (15)
Failure to thrive or weight loss	2 (15)
Ascites	3 (23)
Intestinal obstruction	1 (7.8)
Comorbid conditions [N (%)]	
Atopy (asthma, eczema and seasonal allergies)	7 (54)
Food allergies	5 (38)

Clinical Presentation

Clinical manifestations were variable based on the age, organs involved and the depth of eosinophilic infiltration. All patients had at least one gastrointestinal symptom including abdominal pain (62 %), diarrhea (31 %), nausea and vomiting (31 %) or hematemesis (7.8 %). Patients who had mural and/or serosal disease developed ascites (23 %) (Fig. 2) or intestinal obstruction (7.8 %). Two patients (15 %) had severe mucosal involvement leading to malabsorption; failure to thrive or weight loss and iron deficiency anemia (Table 1). Full clinical presentation for all study subjects is displayed in Supplementary Table 1.

Comorbid Conditions and Peripheral Eosinophilia

Most patients had one or more atopic diseases including asthma, eczema and seasonal allergies (54 %). Prior to diagnosis with EOG, allergy to one or more food items was present in 38 % of the cases (Table 1). Peripheral eosinophilia was present in nine patients (69 %) with a mean peripheral eosinophil % of 19.8 (± 19) (Supplementary Table 2). The mean peripheral eosinophil % was greater in patients with ascites compared to patients without ascites (37.3 $\pm$ 25.4 vs 9.25 $\pm$ 5.4; $P = .01$).

Endoscopic and Surgical Findings

All patients underwent esophagogastroduodenoscopy (EGD), and five patients (38 %) had colonoscopy. The endoscopic exam was normal in seven patients (54 %), and the remaining patients had abnormal endoscopic findings including gastric or duodenal erythema and a gastric ulcer. One patient had jejunal involvement and required antero-grade enteroscopy to establish the diagnosis. Another patient had ileal disease and required laparoscopic full-thickness biopsy for diagnosis (Fig. 2a) after an unremarkable EGD, colonoscopy and antero/retrograde double-balloon enteroscopies. Details on the endoscopic and surgical findings are listed in Table 2.

Histologic Findings

The eosinophilic infiltrate involved more than one organ in four patients. The average number of eosinophils per high-power field was 91.7 $\pm$ 18.4. Histologic findings included eosinophilic cryptitis, eosinophilic abscess and concurrent acute inflammation (Supplementary Table 3). Eight patients had mucosal involvement only (62 %), and three patients had deeper involvement beyond the muscularis mucosa (23 %), and two patients had pan-mural involvement (15 %) (Fig. 3). Two patients had peritoneal fluid analysis showing very high eosinophils (78 and 93 % of total nucleated cells). Pathological characteristics of eosinophilic infiltrate, endoscopic findings and peripheral eosinophilia for all study cases are shown in Supplementary Table 2.

Treatment

Steroid therapy (prednisone, prednisolone or budesonide) was given to six patients (46 %), and one patient (11 %) was treated with a leukotriene receptor antagonist (montelukast), and three patients (23 %) received empiric six-food elimination diet (elimination of milk, soy, wheat, peanuts, eggs and sea food). Elimination of a specific allergenic food was used in three patients (23 %), three patients (23 %) received a combination of two or more therapies, and three patient had spontaneous remission (Table 3). Ten patients (85 %) had clinical follow-up at our institution, of these patients 9 (90 %) had clinical improvement with treatment or had self-limited disease and one patients (10 %) had multiple relapses over 2 years requiring multiple courses of prednisone, and omalizumab could not be used for this case as it was not covered by the patient's medical insurance. Description of the treatment and outcome of individual subjects are provided in Supplementary Table 4.

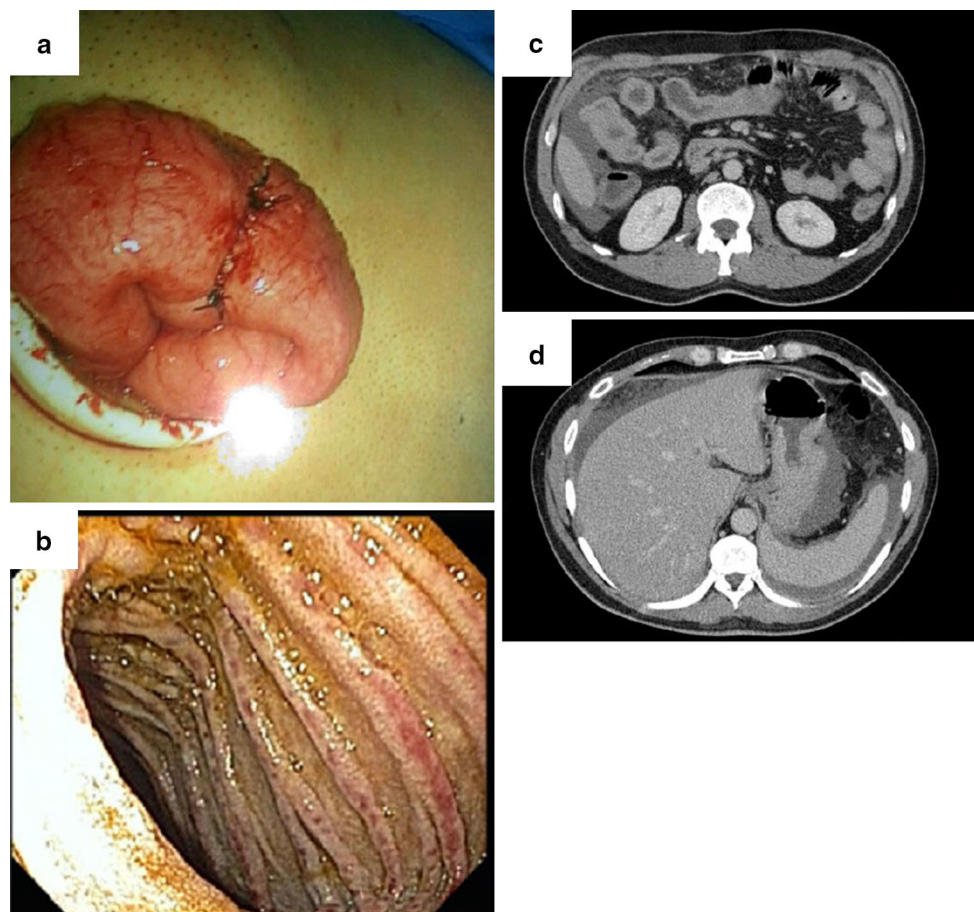


Fig. 2 Erythema and edema of the ileum; wedge biopsy obtained laparoscopically (a). Erythematous jejunal mucosa noted on antero-grade double-balloon enteroscopy (b). Computed tomography of the

abdomen showing diffuse small-bowel wall thickening with small-to-moderate volume small and large bowel intraluminal fluid (c) and moderate volume free fluid (ascites) (d)

Pediatric Versus Adult Patients

There were more males in the pediatric group (75 %) compared to the adult group (20 %) ($P = .17$). Only pediatric patients had failure to thrive or weight loss (50 vs 0 %; $P = .02$), and our findings are consistent with prior studies showing more common weight loss and protein-losing enteropathy in pediatric patients due to predominant mucosal involvement [11]. There was no statistically significant difference in other clinic presentations, comorbid conditions, depth of eosinophilic infiltration or peripheral eosinophilia between the two groups. Three pediatric patients had involvement of two or more organs (75 %) compared to one adult patient (20 %) ($P = .09$) (Table 4).

Discussion

We had 13 cases of eosinophilic gastroenteritis (EOGE) over the last 10 years at our institution with an incidence rate of 18/100,000 endoscopy cases. Seven out of nine

adult cases were females (78 %). The patients' ethnicities were diverse and reflected the population diversity in New Mexico. Clinical presentation was variable, and the most common symptom was abdominal pain (62 %). Other symptoms and signs including diarrhea, nausea, vomiting, hematemesis, microcytic anemia, failure to thrive, weight loss, ascites and intestinal obstruction occurred in less than one-third of the patients. Only pediatric patients had failure to thrive or weight loss 2(50 %). Most patients (54 %) had associated atopic disease, and 38 % had prior food allergies. Peripheral eosinophilia was seen in 69 % of patients with a mean eosinophils count four times higher in patients with associated ascites ($P = .01$). To establish diagnosis, one patient required antero-grade balloon enteroscopy and one patient required a laparoscopic biopsy.

Most patients (54 %) had normal endoscopic findings, and endoscopic abnormalities were non-specific and included gastric, duodenal and jejunal erythema and a gastric ulcer. All patients had mucosal involvement, and 38 % of patients had deeper eosinophilic infiltration. Four

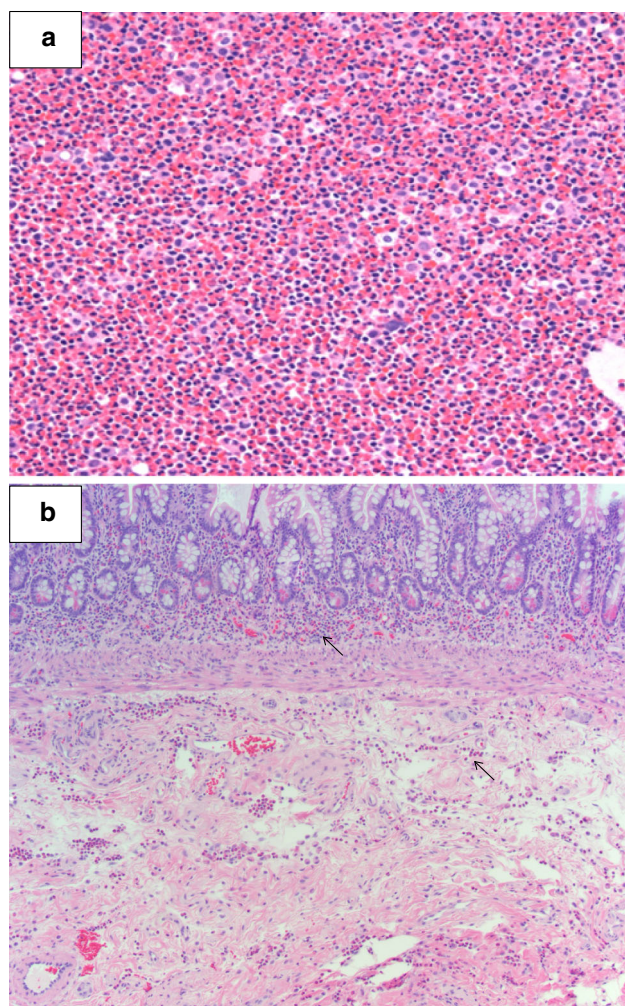


Fig. 3 Cell block specimen of the ascites fluid demonstrates numerous eosinophils (a). Full-thickness ileal resection specimen showing high-density eosinophil infiltrates aggregating in the deep mucosa and submucosa (arrows) (b)

patients had more than one organ involvement. Outcomes of our study cohort were similar to what was reported in the literature; of the ten patients (77 %) who had long-term follow-up, six patients responded to treatment with steroids and/or diet restriction and three patients had spontaneous remission. One subject had recurrent flares requiring multiple courses of prednisone therapy.

Limited number of EOG cases have been reported in the literature, previous studies by Talley et al. and De Chambron et al. included about 80 cases [12, 29] and showed slight male predominance with a male-to-female ratio (M/F ratio) of 1.3–1.4:1, and based on these studies EOG is thought to have similar epidemiology to eosinophilic esophagitis (EOE) which is clearly a male-predominant disease (M/F ratio of 3:1) [14, 30]. However, a recent study [4] by Reed, et al. showed only 18 % males in 11 adult cases of EOG and few other studies showed mild

Table 2 Endoscopic procedures, findings and depth of eosinophilic infiltrate

<i>Procedures and their findings</i>	
EGD ^A [N (%)]	13 (100)
Normal	7 (54)
Gastric erythema	5 (38)
Gastric ulcer	1 (7.8)
Duodenal erythema	1 (7.8)
Colonoscopy	5 (38)
Normal	5 (100)
Anterograde enteroscopy	1 (7.8)
Erythematous dilated mid-jejunum ^B	
Double-balloon enteroscopy followed by laparoscopy	1 (7.8)
Small intestinal wall edema ^{C,D} , erythema and large-volume ascites ^{E,F}	
<i>Depth of eosinophilic infiltrate</i>	
Mucosal	8 (62)
Submucosal	3 (23)
Panmural ^G	2 (15)

^A EGD esophagogastroduodenoscopy

^B Figure 2b

^C Figure 2a

^D Figure 2c

^E Figure 2d

^F Figure 3a

^G Figure 3b

female predominance (38–45 % males in 55 adult cases) [16, 24] or no gender predilection [31].

The findings of our study suggest that EOG might be underdiagnosed and that more cases are being diagnosed with the wider use of endoscopy. The incidence rate of 18 per 100,000 endoscopies is consistent with more recent studies [4, 32]. The epidemiology of EOG is not well established given the limited number of reported cases, but it appears that there might be slight female predominance or no gender predilection in adults, as opposed to eosinophilic esophagitis (EOE) which has a marked male predominance. The clinical presentation is variable, and the diagnosis requires high clinical suspicion. Advanced endoscopy (enteroscopy) or laparoscopic surgery might be required to make the diagnosis in patients with jejunal or ileal involvement and in cases with deep eosinophilic infiltration. Most patients responded well to prednisone and/or diet restriction therapy.

Limitations

The number of cases in this study was small (13 cases) with only four pediatric cases, and this made the distinction of

Table 3 Treatment and outcomes for eosinophilic gastroenteritis patients

Treatment [<i>N</i> (%)]	
Budesonide	1 (11)
Prednisone/prednisolone	5 (38)
Montelukast	1 (11)
Six-food elimination diet	3 (23)
Elimination of allergenic food	3 (23)
Combination of two or more therapies	3 (23)
Spontaneous remission	3 (23)
Follow-up duration in months (mean $\pm$ SD; range)	5.8 $\pm$ 7.1; 0–24
Number of endoscopies (mean $\pm$ SD; range)	2.1 $\pm$ 1.3; 1–6
Outcome in patients who had follow-up [<i>N</i> (%)]	
Clinical improvement with therapy	6 (60)
Spontaneous remission	3 (30)
Recurrent flares	1 (10)

Table 4 Comparison between pediatric and adult patients

	Pediatric patients	Adult patients	<i>P</i> value
Male [<i>N</i> (%)]	3 (75)	2 (22)	.17
Race			
White	3 (75)	4 (44)	.30
Other races	1 (25)	5 (56)	.21
Clinical presentation [<i>N</i> (%)]			
Microcytic anemia	1 (25)	2 (22)	.90
Failure to thrive/weight loss	2 (50)	0 (0)	.02
Ascites	0 (0)	3 (33)	.18
Intestinal obstruction	0 (0)	1 (11)	.48
Abdominal pain	1 (25)	7 (78)	.07
Diarrhea	1 (25)	3 (33)	.76
Nausea and vomiting	1 (25)	3 (33)	.76
Hematemesis	1 (25)	0 (0)	.11
Comorbid conditions [<i>N</i> (%)]			
Atopy (asthma, eczema and seasonal allergies)	2 (50)	5 (56)	.85
Food allergy	3 (75)	2 (22)	.07
Depth of eosinophilic infiltration [<i>N</i> (%)]			
Mucosal	4 (100)	9 (100)	–
Muscularis mucosa/submucosa	0 (0)	4 (44)	.10
Serosa	0 (0)	2 (22)	.30
Organ involvement [<i>N</i> (%)]			
More than one organ	3 (75)	1 (20)	.09
Esophagus	2 (67)	0 (0)	–
Stomach	2 (50)	6 (75)	.39
Duodenum	1 (25)	1 (33)	.80
Jejunum	0 (0)	1 (50)	–
Ileum	1 (100)	1 (100)	–
Colon	3 (100)	1 (33)	.08
Peripheral eosinophilia			
EOGE ^a patients with eosinophilia [<i>N</i> (%)]	2 (67)	7 (88)	.70
Eosinophils% (mean $\pm$ SD)	8.67 $\pm$ 9.02	19.57 $\pm$ 22.47	.45

^a EOGE eosinophilic gastroenteritis

the clinical presentation and histologic features and outcomes between the adult and pediatric groups limited. Another limitation is that only ten patients had long-term follow-up.

Diet restriction treatment has been shown to be effective in EOG, and in a recent study [4] a 57 % response rate to diet restriction was noted; however, many patients were on simultaneous steroid therapy. Good response to amino acid-based formula and seven-Food empiric dietary restriction in most patients was noted in a pediatric study [5]. More data are needed on the efficacy of diet restriction in adult patients with EOG, if proven effective; diet restriction will help avoiding the side effects of steroid therapy. In summary, this retrospective cohort study of EOG provides additional epidemiological and outcome data to what is known about this rare condition. More studies are needed regarding the epidemiology, pathophysiology and long-term outcomes of EOG.

Compliance with ethical standards

Conflict of interest None.

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